Unregistered and off-label medicine use in highly specialised paediatrics at Tygerberg Hospital

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

Introduction: Off-label (OL) medicine use in children is a common practice not yet extensively investigated in Africa.

Aim: The aim of the study was to determine the extent of unregistered (UR) and OL medicine use in inpatients admitted to highly specialised paediatric wards at a tertiary hospital in South Africa.

Objectives: The primary objective of the study was to determine the frequency of UR and OL medicine events in highly specialised paediatrics. The secondary objective was to determine the most frequently prescribed UR and OL medicines per paediatric subspecialty.

Respondents and methods: This was a prospective descriptive study over a period of three months (October to December 2011), documenting all medicines prescribed to children (under 18 years) admitted for highly specialised inpatient care to Tygerberg Hospital in Parow, Cape Town. Patients were classified into four age groups: newborns (0–27 days), infants (28 days to 23 months), children (2–11 years) and adolescents (12–18 years). Data collected included demographic data, diagnostic data and data concerning all medicine events. Data analysis of medicine events included registration status (defining extemporaneous use as UR use) and OL use according to dose, frequency, route of administration, age and indication.

Results: There were 1 514 medicine events for 199 children (mean age?; range), with an average of 7 medicines per child (range 1–28). The majority of the medicine events were in the age category infants (44%), followed by children (42%), adolescents (8%) and neonates (6%). Nearly half (49%) of all the medicine events were either UR (20%) or OL (29%). Almost a quarter (22%) of the patients received a UR medicine, 68% an OL medicine and 24% both a UR and an OL medicine. The most common reason for OL medicine use was dose for weight (22.2%), while extemporaneous use as UR use involved 5% of all medicine events. Extemporaneous use (23%) and OL use (42%) were particularly common in paediatric infectious diseases, especially for antituberculosis medicines, reflecting the burden of paediatric disease due to tuberculosis and also confirming that few of these medicines have been tested in children.

Conclusions: OL and UR medicine use is common in highly specialised paediatrics in South Africa, especially for children with infectious diseases. The findings indicate the need for dedicated paediatric clinical trials in South Africa to establish safety and efficacy data, especially to improve

paediatric medicine formulations.

Opsomming

Inleiding: Die gebruik van niegoedgekeurde (NG) medisyne by kinders is ’n algemene praktyk wat nog nie uitvoerig in Afrika ondersoek is nie.

Oogmerk: Die oogmerk van die studie was om die omvang te ondersoek van die gebruik van ongeregistreerde (OR) en NG medisyne by hospitaalpasiënte wat in hoogs gespesialiseerde pediatriese sale by ’n tersiêre hospitaal in Suid-Afrika opgeneem is.

Doelstellings: Die primêre doelstelling van die studie was om die frekwensie van gebeure rakende OR en NG medisyne in hoogs gespesialiseerde pediatrie te bepaal. Die sekondêre doelstelling was om te bepaal watter OR en NG medisyne die gereeldste per pediatriese subspesialiteit voorgeskryf word.

Respondente en metodes: Hierdie studie was ’n prospektiewe beskrywende studie oor ’n tydperk van drie maande (Oktober tot Desember 2011), waarin alle medisyne wat voorgeskryf is aan kinders (jonger as 18 jaar) wat vir hoogs gespesialiseerde hospitaalsorg by Tygerberg Hospitaal in Parow, Kaapstad, opgeneem is, opgeteken is. Pasiënte is in vier ouderdomsgroepe geklassifiseer: pasgeborenes (0–27 dae), babas (28 dae tot 23 maande), kinders (2–11 jaar) en adolessente (12–18 jaar). Data wat ingesamel is, het ingesluit demografiese data, diagnostiese data en data oor alle medikasiegebeure. Data-ontleding van medikasiegebeure het ingesluit registrasiestatus (waarin geïmproviseerde gebruik as OR gebruik gedefinieer is) en NG gebruik volgens dosis, frekwensie, toedieningsmetode, ouderdom en indikasie.

Resultate: Daar was 1 514 medikasiegebeure vir 199 kinders (gemiddelde ouderdom?; bestek), met ’n gemiddelde van 7 medisynes per kind (bestek 1–28). Die meerderheid medikasiegebeure was in die ouderdomskategorie van babas (44%), gevolg deur kinders (42%), adolessente (8%) en pasgeborenes (6%). Bykans die helfte (49%) van al die medikasiegebeure was óf OR (20%) óf NG (29%). Byna ’n kwart (22%) van die pasiënte het OR medisyne ontvang, 68% NG medisyne en 24% sowel OR as NG medisyne. Die algemeenste rede vir die gebruik van NG medisyne was dosis vir gewig (22.2%), terwyl geïmproviseerde gebruik as OR gebruik by 5% van alle medikasiegebeure betrokke was. Geïmproviseerde gebruik (23%) en NG gebruik (42%) was veral algemeen by pediatriese aansteeklike siektes, veral vir antituberkulose-medisyne, wat die las van pediatriese siektes weens tuberkulose weerspieël en ook bevestig dat min van hierdie medisyne by kinders

getoets is.

Gevolgtrekkings: Die gebruik van NG en OR medisyne is algemeen in hoogs gespesialiseerde pediatrie in Suid-Afrika, veral by kinders met aansteeklike siektes. Die bevindinge dui op die behoefte aan toegewyde pediatriese kliniese toetse in Suid-Afrika om veiligheids- en doeltreffendheidsdata te verkry, veral om pediatriese medisyneformulering te verbeter.

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Glossary

Adolescent: Paediatric patient aged older than 11 and younger than 18 years, defined as used in study.[53]

Adverse medicine reaction: A noxious and unintended response to a medicine that occurs at normal therapeutic doses used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function.[12]

AIDS: Acquired immunodeficiency syndrome.

Central/tertiary hospitals: Hospitals in South Africa that provide both general specialist services and highly specialised (Level 3) services.[54]

Child: Paediatric patient aged 2–11 years, defined as used in study.[53]

Excipients: Inactive pharmaceutical ingredients utilised in extemporaneous medicine compounding.[26]

Extemporaneous compounding: Refers to the manipulation or compounding of a manufactured medicine (crushing of tablets or opening of capsules and suspending the contents in fluid), resulting in a change in the form or properties of the manufactured medicine, or the manufacturing of a medicine from raw products by a production pharmacist.[26]

Highly specialised paediatrics: Medical care provided to children by subspecialist paediatricians.

HIV: Human immunodeficiency virus.

HAART: Highly active antiretroviral therapy.

Infant and toddler: Paediatric patient older than 27 days and younger than 2 years.[53]

Manipulation: Breaking a tablet or splitting a capsule at the time of administration, a subcategory of extemporaneous compounding.[26]

Medicine: Any pharmacological agent prescribed and administered to a patient; this excludes intravenous fluid therapy and blood transfusions.

Medicine event: A single prescription of an individual medicine on a prescription chart of a patient.

Medicines Control Council: The national regulatory body for medicine registration.

Neonate: Paediatric patient aged 0–27 days.[53]

Off-label (OL) medicine: Medicine prescribed outside the terms and conditions of the product license.[47]

Pharmacodynamics: The study of the effects of medicine on the body.

Pharmacokinetics: The study of the mechanism by which a medicine is absorbed, distributed, metabolised and eliminated by the body.

Regional hospitals: Hospitals in South Africa that provide general specialist care (Level 2) services.[54]

Special formulations: These are medicines already registered in one form but reformulated under a special license to meet the therapeutic needs of a patient.

Subspecialist: A paediatrician who has further specialised in a particular clinical area of paediatrics.

Unregistered medicine (UR): A medicine that is prescribed but not registered with the national regulatory authority.[47]

Chapter 1: Introduction

1.1 Background and context

The registration of medicines is overseen by national regulatory systems, which in South Africa is the Medicines Control Council (MCC).[1,2] These regulatory bodies ensure that medicines are tested for safety, efficacy and quality prior to public marketing and utilisation.[3,4] The gold standard for adult medicine is the proven safety and efficacy data generated through adequate clinical trials.[5] Unregistered (UR) medicine use refers to a medicine that is prescribed but not registered with the national regulatory system, while off-label (OL) medicine use refers to the practice of prescribing a registered medicine outside of the conditions for which it is registered.[2] OL medicine use can pertain to age, dose, formulation, route, frequency or not being registered for a specific indication.[6] OL and UR medicine use is common in paediatric medicine, especially neonatology and paediatric critical care.[7] This practice is raising concern globally, as documented in studies from Europe, the United States of America (USA) and Brazil,[8] as up to 75% of medicines prescribed to children worldwide are OL.[9] OL and UR medicine use may offer therapeutic benefit, may have no therapeutic effect or may result in adverse medicine events.[10] The documented increased risk of adverse medicine events[11,12,13,14] and medication errors[15] with OL medicine use is a cause for concern. However, clinicians' reluctance to prescribe a UR or an OL medicine may also deprive a child of potentially effective treatment.[10]

The practice of prescribing UR or OL medicine is due to a lack of paediatric-specific scientific data derived from clinical trials to satisfy the national registering requirements with regard to efficacy and safety.[5] Such utilisation is not always inappropriate and may be justified within a specific clinical context.[5] For example, in paediatric oncology, the OL and UR use of medicines and biological products forms an essential part of many internationally standardised treatment protocols.[16] Similarly, in paediatric cardiology, the first-line treatment for maintaining ductal patency in duct-dependent congenital cyanotic heart lesions is prostaglandin.[17] In autoimmune and inflammatory central nervous system disorders, the OL use of rituximab was demonstrated to improve neurological outcomes.[18] Other considerations that need to be taken into account are prescriber awareness,

litigation fears, parental and child awareness, and the risk-benefit ratio based on the clinical indication when medicines are prescribed OL.[19,20] With this study, we wanted to determine the extent of OL and UR medicine use in highly specialised paediatrics in a single central/tertiary hospital in South Africa, as there is a paucity of published data from Africa.

1.2 Literature review

Licensing ensures that medicines are tested in rigorous clinical trials for safety, efficacy and quality prior to public use.[21] Pharmacotherapeutic tragedies that exposed children to the adverse effects of inadequately studied medicines prompted the development of medicine regulation.[1] In 1901, for example, diphtheria toxoid contaminated with tetanus resulted in the deaths of 13 children.[22] OL use of the sedative thalidomide in the first trimester of pregnancy for pregnancy-induced vomiting resulted in miscarriages, stillborn infants and multiple birth defects, including phocomelia.[23] Historically, chloramphenicol administered to neonates resulted in grey baby syndrome.[24] The characteristic grey discolouration, cyanosis, vomiting, acidosis and hypothermia were due to age-related deficiency in glucuronide conjugation, the main pathway for chloramphenicol excretion. These complications can be prevented with lower doses administered, decreased frequency of medicine administration and therapeutic medicine monitoring.[24] Diethylene glycol, a diluent used in the manufacturing of elixirs, has resulted in the deaths of children on more than one occasion.[24] In 1937, 34 children succumbed to toxicity-related adverse reactions. This tragedy repeated itself in Nigeria (1990 and 2009), Bangladesh (1990 and 1992) and Haiti (1995 and 1996).[24] Most recently in 2011, lopinavir/ritonavir use in premature infants exposed them to ethanol/propylene toxicity.[9] Due to these adverse events, medicine safety communication resulted in a change in lopinavir/ritonavir labelling in 2011.[9]

Children have been referred to as ‘therapeutic orphans’ as a large number of medicines utilised in the clinical management of children are lacking in scientific evidence to support their paediatric use.[21] The growing global concern about this matter is evidenced by the growing number of studies documenting the extent of UR and OL medicine use.[8,11,25] Globally up to three-quarters (40–60%) of medicines used in children in the European Union (EU) and two-thirds in the USA are used OL.[7,8,9]

The definitions of UR and OL medicine use differ widely in the literature, making direct comparisons among various studies difficult.[7] According to Conroy et al[5] and Turner et al,[26] a UR medicine is a medicine that has not received marketing authorisation, while OL medicine utilisation refers to the use of a medicine outside the terms of the product registration. The authors categorise extemporaneous preparations, formulations manufactured under a special license and medicines without a stated dose for a particular age group as UR medicines.[6] Extemporaneous compounding is the process whereby a manufactured product is manipulated or compounded into a different formulation or a new product is manufactured from raw ingredients in a manufacturing pharmacy.[26] Extemporaneously compounded medicines can be categorised as UR medicine use as compounding of medicines removes the regulatory safeguards, unless such manipulation or compounding is specifically covered in the product's package insert.[27] Medicines that are extemporaneously compounded or manipulated are not subjected to the regulatory safeguards that ensure the quality, safety and efficacy of the specified use during the registration process; therefore, prescribers and pharmacists cannot make assumptions about the quality, safety and efficacy of these medicines.[28] Consensus on the definition of these terms for utilisation for research and regulatory purposes was recently reached through a Delphi survey.[6] According to this survey, extemporaneously compounded medicines and medicines manipulated at the time of administration are classified as OL medicines.[6]

OL and UR medicine use is common in all paediatric clinical settings, including neonatal and paediatric intensive care units, paediatric inpatients, emergency paediatrics and ambulatory paediatrics.[4] Several systematic reviews,[7,8,25] multicentre studies[29,31] and single-centre[30] studies have evaluated the extent of UR and OL medicine use in different clinical settings (paediatric wards, intensive care units, ambulatory care and primary health care).[7,8,25-31,35] OL medicine use ranged from 7% to 70% of paediatric medicine events,[7,8,25,35] while UR medicine use ranged from 0.2% to 48%.[8,25,35] The percentage of children exposed to an OL or a UR medicine event ranged from 42% to 100%.[8] The main reason for OL use was dose,[7,8,30,35] followed by age,[7,8,30] lack of paediatric data,[8] frequency and formulation.[35] These findings were confirmed by recent studies (last five years) documenting UR and OL medicine use in hospitalised children in Australia,[32] Finland,[33] Croatia[10] and Palestine.[34] The study designs varied from retrospective[32] to prospective studies[33,34] and included

one cross-sectional survey.[10] Consistent among all these studies was that OL medicine use (13.3–71%) was more common than UR medicine use (2.6–35.3%)[10,32,34] and that the most common reasons for OL medicine use were dose and age, especially in neonates and young children.[10,32-34]

Younger children, especially neonates, were subjected to the highest percentage of UR and OL medicine events.[7,8] The number of neonates exposed to at least one OL or UR medicine ranged from 80% to 100% versus 32% to 62% for children.[7] The most common subgroups of medicines used OL in neonates, according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, were cardiovascular medicines, anti-infectives for systemic use and medicines acting on the central nervous system.[7,8,25,30,31] In neonatal critical care, the proportion of medicine events that were UR ranged from 10% to 62% and for OL use from 14% to 63%.[36,37,38]

Conroy et al conducted a prospective multicentre international survey of paediatric wards in five European countries and found that nearly half of all medicine events (46%) were either UR or OL (7.3% UR; 38.5% OL).[35] The most common reasons for OL medicine use were dose, frequency and formulations. Paracetamol was the most frequently prescribed medicine in most of the centres, while the most frequently used OL medicines differed widely among centres, including the following: paracetamol, salbutamol, budesonide, beclometasone and cyclizine.[35]

An investigation of UR and OL medicine use in paediatric pain management in a prospective study found that paracetamol was the most frequently used analgesic and accounted for 40% of medicine events, followed by brufen (20%) and codeine phosphate (11%).[39] Diclofenac, pethidine and morphine each accounted for 7% of medicine events. All the medicine events for pethidine (100%), 98% for diclofenac, 79% for morphine and 30% for paracetamol were OL.[39] The most common reason for OL use was dose (12%). OL use for route, age and indication each accounted for 7% and weight for 1% of medicine events.[39]

The clinical trials evaluating the OL use of omalizumab, a recombinant DNA-derived monoclonal antibody registered for the treatment of moderate and severe persistent asthma and chronic spontaneous uticaria in adults and children (more than 6 years in the EU and more than 12 years in

the USA), found it to be efficacious and well tolerated for the treatment of seasonal allergic rhinitis, with efficacy being enhanced when combined with subcutaneous immunotherapy as example of OL use for indication.[40] Treatment for other OL indications such as allergic broncho-pulmonary aspergillosis, nasal polyps, severe refractory atopic dermatitis, and food allergy and anaphylaxis is currently not supported by paediatric literature, despite growing popularity of the OL use of this medicine.[40]

Published data on the extent of UR and OL medicine use in developing countries and sub-Saharan Africa is limited. In Nigeria, nearly half (41.9%) of the medicines prescribed to children aged 0–5 years in a tertiary and a primary health care centre were UR and OL. Overall, one-fifth (20.4%) of medicine events were either UR or OL (21.5%).[41] OL medicine use was more frequent in the tertiary health care centre (24%) compared to the primary health care centre (18.7%), while UR medicine use was more common in the primary health care centre (27.5%) compared to the tertiary health care centre (13.9%).[41] The most common reason for UR medicine use was extemporaneously prepared medicines, while dose was the most common reason for OL medicine use.[41] The most frequently used ATC classification medicine subclasses were antibacterial agents, antiprotozoal agents, analgesics, vitamins and haematopoietic medication in both centres, which correlates with the profile of diseases treated most frequently, namely malaria and other infectious diseases (respiratory tract infections, gastroenteritis, sepsis and HIV/AIDS) that can present with pyrexia and anaemia.[41] Paracetamol use accounted for 12.1% of all medicine events, although the exact frequency of UR and OL use of individual medicines was not reported. A limiting factor of this study was the retrospective nature and insufficient patient medical, medication and demographic data.[41]

Although there are reports of UR and OL use of specific medicines in South Africa, published data on the extent of UR and OL medication in the different clinical settings is lacking. A survey of intravenous immunoglobulin use at a tertiary paediatric health care centre found that more than half the intravenous immunoglobulin utilisation (59%) was OL for indication.[42] The most frequent clinical indications for OL use were infections and post organ transplant.[42] OL medicine use was most frequent in children aged more than five years, accounting for nearly half (46%), followed by

children aged less than a year (29%), while those aged 1–5 years accounted for a quarter (25%) of OL medicine events.[42]

Dinoprostone (prostaglandin E2 receptor agonist) is registered in South Africa for the induction of labour but is used OL to provide lifesaving emergency treatment by maintaining ductal patency when administered to newborns suffering from duct-dependent congenital cyanotic cardiac lesions, as well as long-term treatment of low-birth-weight infants with duct-dependent pulmonary circulations not yet meeting the criteria for corrective shunt surgery.[17] In 2009, no warning was given to clinicians about the national shortage of this lifesaving medicine in both the public and the private sector, due to legislative constraints as the medicine is not registered for such use.[17] This led to a serious shortage of this lifesaving medicine, proving the necessity to conduct clinical trials to ensure registration of this medicine for this indication in South Africa.[17]

Children have specific therapeutic needs that need to be addressed as they are not small adults.[9] Extrapolation of data from adults to children is not possible due to age-related differences in physiology and disease pathophysiology.[22] Children demonstrate physiological variations in pharmacokinetics and pharmacodynamics corresponding to the different developmental stages of childhood. These factors affect the absorption, distribution, metabolism and excretion of medicines. Significant dose adjustments may be required to target similar plasma concentrations as in adults.[3] It is therefore necessary to ensure that scientifically based age-related dosing information is available as treatment failure can result from subtherapeutic doses and adverse effects without any therapeutic benefit from doses higher than required.[32]

Children also require medicine formulations that are appropriate for the developmental age of the child, and medicine palatability is an especially important factor in children.[9] Palatability may affect adherence and subsequently treatment outcome.[9] It is common practice, due to the unavailability of suitable age-appropriate formulations, for medicines to be prepared extemporaneously (compounding medication from ingredients within a pharmacy), or the dose, form or route of a medicine may be manipulated. This practice raises safety concerns, and efficacy may be compromised.[9] There is an environmental risk, especially with the handling of cytotoxic and

biological medicines, and an individual occupational risk for the health care provider.[9] Manipulated medicines and extemporaneous preparations are not well supported by pharmacokinetic and pharmacodynamic data, nor is there sufficient data to validate tolerability, stability and reproducibility. These factors make medicine use in this manner unsafe.[9]

Clinical trials are the gold standard to generate scientific data to support a medicine's safety profile, efficacy and quality prior to registration, public marketing and use.[3] Conducting clinical trials in the paediatric subpopulation is, however, challenging, especially due to children's vulnerability.[3] Reasons for the lack of paediatric clinical trials include the small commercial market for children, the lower projected commercial gains, as well as litigation fears.[3] There are also ethical concerns, especially related to possible harm, the complex consent process including parental consent as third-party consent and smaller numbers of participants.[3]

The risk of adverse medicine reactions[11-13,26] and medication errors[15] is increased with UR and OL medicine use.[11-13,15,26] According to the WHO, an adverse medicine reaction is defined as "an effect that is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis and therapy".[12] Neubert et al reported that the overall incidence of adverse medicine reactions was 17.4%,[12] while Turner et al found it to be 9.9%.[26] The incidence of an adverse medicine event associated with UR and OL medicine use was 6% respectively in both studies, compared to that of adverse medicine events associated with registered medicine use at 5.6% (Neubert et al)[12] and 3.9% (Turner et al).[26] Bellis et al[11] and Santos et al[43] found that the relative risk of an adverse medicine reaction was increased 1.67 fold and 2.4 fold for a UR or an OL medicine course respectively compared to a registered medicine.[11,43] The other safety concern is the association of registration status with medication errors (prescribing, dispensing, labelling or administration). Conroy et al found that compared to registered medicine use, a UR medicine was more likely to be associated with errors.[15] The error rate was higher in neonatal wards (38%), and the risk of a medication error was increased 5.8 fold compared to the error rate in paediatric wards (17%), with a 2.2-fold increased risk of a medication error.[15] The degree of harm caused by the medication error was graded according to the United Kingdom (UK) National Patient Safety Agency definitions, with more than half (60%) of the medication errors causing moderate harm being associated with UR (25%) or OL medicine

(35%) use.[15] Medication errors that caused moderate harm were 2.8 times more likely to be associated with a UR and an OL medicine compared to a registered medicine. No medication errors caused severe harm or death.[15]

The views of children and health care providers' experiences with and attitudes towards UR and OL prescribing and paediatric clinical trials are important. Mukkattash et al reported that healthy school children aged 10–16 years in focus group discussions were of the opinion that UR and OL medicine use was unsafe and unethical and advocated for medicine testing to assist in the licensing of medicines for children.[44] Health care providers expressed familiarity with UR and OL medicine use, mainly through personal experience. Despite safety and efficacy concerns in the majority, only 30% of practitioners informed parents about their safety and efficacy concerns, 56% believed that clinical trials were necessary for medicine evaluation and only 28.3% were willing to be part of clinical research.[44]

Due to the overwhelming evidence and documentation of the extent of UR and OL medicine use, legislators in the USA and Europe have implemented paediatric regulations in an effort to improve the development of safe and effective medication for children.[24,45] The USA has led this effort with two significant outcomes resulting from multiple legislation and policy amendments: The first action taken was a six-month extension of patency (Food and Medicine Modernisation Act, 1997 and Best Pharmaceuticals for Children's Act [BPCA], 2002), and the second action was the mandatory provision of paediatric data and labelling instructions by pharmaceutical companies for new medicines, biological, addition of new indications, dose forms and regimens for any medicine with the potential for paediatric use (Pediatric Research Equity Act [PREA], 2003).[24] The BCPA and PREA were reinstated in 2007 as part of the Food and Drug Administration Amendments Act, 2007.[24] Europe has also implemented legislative changes.[46] The European Commission enacted the EU Paediatric Regulation 1901/2006 on medicinal products for paediatric use.[46] Pharmaceutical companies are now required to submit a Paediatric Investigation Plan, and as reward they will be granted a six-month extension of the medicine patent. The European aim is to generate paediatric data without exposing children to unnecessary clinical trials or delaying the registration of adult medicines.[46]

Legislative changes have had an impact on UR and OL medicine use in children. Osuagu et al compared prelegislation OL and UR medicine use (2001) to postlegislation OL and UR medicine use (2011).[33] The overall percentage of UR medicine use remained stable at 13%, but there was an increase in the proportion of patients who received at least one UR medicine from 26% in 2001 to 53% in 2011.[33] There was at least one event per patient for UR or OL use in 79% of patients in 2011 versus 58% in 2001.[33] Fortunately, there was a decline in extemporaneous preparations from 33% in 2001 to 10% in 2011.[33] OL medicine use increased from 36% in 2011 from 42% in 2001. The most common reasons for OL medicine use in 2001 were the absence of paediatric information (38%) and route (34%), compared to 2011 when the main reasons were dose (17.3%) and age (9.9%).[33] The positive effects of legislation are reflected in the decrease in extemporaneous compounding and a change in the most common reason for OL medicine use, namely the absence of paediatric information (2001) versus dose (2011).[33]

The MCC is the statutory body in South Africa that regulates medicine registration and was established in terms of the Medicines and Related Substances Control Act 101 of 1965.[2,47] Registration of a medicine is possible if the necessary safety, quality and efficacy data from clinical trials for specified indications are available.[2,47] In South Africa, Regulation 45(3) of the Medicines and Related Substances Control Act 101 of 1965 does not allow the distribution of information regarding OL medication, and Section 20(1)(b) prohibits the advertising of claims of therapeutic efficacy and effect other than those that the product registration satisfies. There is legislative control of medicine advertising according to the approved marketing license, which may place health care providers at an information disadvantage as information on OL medicine use may not be distributed by pharmaceutical or distribution companies.[48] This also serves as protection for consumers and patients, especially limiting possible misleading information, expansion of indications, exaggeration of efficacy or de-emphasis of serious adverse events.[1]

To generate information about the practice of UR or OL medicine use in highly specialised paediatrics in South Africa, we conducted a prospective descriptive survey at Tygerberg Hospital, a central/tertiary hospital in Parow, Cape Town, South Africa.

Chapter 2: Aim and methodology

2.1 Aim and objectives

2.1.1 Study aim

The aim of the study was to prospectively document the UR and OL medicine use in children admitted to highly specialised paediatric wards at Tygerberg Hospital over a three-month period.

2.1.2 Study objectives

The primary objective of the study was to determine the frequency of UR and OL medicine events in highly specialised paediatrics. The secondary objective was to determine the most frequently prescribed UR and OL medicines per paediatric subspecialty.

2.2 Research question and hypothesis

The research question was what the extent and nature of UR and OL medicine use in highly specialised paediatrics (tertiary health care) at Tygerberg Hospital were.

Hypothesis: UR and OL medicine use in highly specialised paediatrics at Tygerberg Hospital is a common practice.

Null hypothesis: UR and OL medicine use in highly specialised paediatrics at Tygerberg Hospital is an uncommon practice.

2.3 Study design and setting

This was a prospective descriptive survey conducted over three consecutive months between 1 November 2010 and 31 January 2011 in the highly specialised paediatric wards at Tygerberg Hospital, where there is a combination of general paediatric and highly specialised paediatric wards, as well as critical care wards for neonatology and paediatrics respectively. The highly specialised wards include beds for paediatric cardiology, endocrinology, gastroenterology, infectious diseases, nephrology, neurology, oncology, haematology, pulmonology, rheumatology and immunology. There are a total of 275 paediatric beds at Tygerberg Hospital, with 139 beds for highly specialised

paediatrics. This study was a substudy of a larger study documenting UR and OL medicine use in children admitted to Tygerberg Hospital. A prospective study design was suitable as the objective of the study was to determine exposure to an event (UR or OL medicine use) in the selected subjects/cohort admitted to highly specialised paediatric wards.

2.4 Data collection and management

The medicine charts of all children aged 0–16 years admitted to the highly specialised wards at Tygerberg Hospital during the study period were reviewed daily in the survey. The data was collected by the investigator only, after hours (between 4 and 7 pm) daily, over three consecutive months. Medical staff was informed about the study and the data collection but was not involved in the process of data collection. No identifiable data was collected, but each record received a unique study number that could be linked to the original patient record. Data was captured daily by the investigator in electronic format (Microsoft Excel) on a hand-held iPad. The following data was collected: demographic data (age, weight, sex and diagnosis) and data on medicines (pharmacological substances prescribed and administered to patients, excluding intravenous fluid, blood and blood products, and total parental nutrition) prescribed (medicine name, dose, frequency, formulation and route of administration). Information on total parental nutrition, intravenous fluid, blood and blood products prescribed was not collected. At the end of the patient's admission period to the ward, completed data capture sheets were transferred to a study database on a central computer, analysed and imported into SSPS Version 19 for statistical analysis.

2.5 Ethical considerations

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, at Stellenbosch University. A waiver of consent was granted by the Ethics Committee as no identifiable data was collected and the study posed minimal risk. The custodian of the hospital provided consent for access to patient files.

2.6 Definition of the terms 'unregistered' and 'off-label'

The Delphi survey proposed a definition of UR and OL medicine use for the purpose of research and regulation.[6] However, the definition of UR and OL medicine use in published clinical studies documenting the extent of UR and OL medicine use is based on the definition by Turner,[25] Conroy[5,35,38] and Ernest.[27] Extemporaneous medicine use is the defining category for both definitions. In the Delphi survey, extemporaneous medicine use is defined as OL,[6] while in the definition by Turner,[26] Conroy[5,35,38] and Ernest,[27] extemporaneous use, if not added to the package insert, is defined as UR. During data analysis in this study, both definitions were used and reported in the results section.

2.7 Data analysis

The 2012 South African Medical Formulary[50] manufacturer's package insert and the January–February 2013 edition of the MIMS desk reference[51] were used as reference sources for data analysis. Each medicine event per patient was analysed and categorised as either (i) registered with the MCC and appropriately used; (ii) UR with the MCC; or (iii) OL medicine use as a medicine used outside the authorised product registration with the MCC. OL medicine use can be further divided into one of the following six categories: (i) OL for age; (ii) OL for dose; (iii) OL for route of administration; (iv) absence of paediatric information; (v) indication: a medicine used to treat an illness not covered by the MCC registration; and (vi) contraindication: a medicine utilised in the paediatric population despite documented contraindication for age group.

Extemporaneous compounding and medicine manipulation (e.g. crushing of tablets or opening of capsules and suspending them in a liquid formulation) is a special category of medicine use and was analysed according to the definition by Conroy,[5,35,38] Turner[26] and Ernest[27] (extemporaneous compounding is classified as UR) and then according to that of the Delphi survey[6] (extemporaneous compounding is classified as OL). Extemporaneous compounding included any manipulation of a medicine at the time of administration or compounding of a registered medicine, resulting in a change in formulation, or manufacturing of a medicine from raw ingredients.[27] Extemporaneous

manipulation was done by a pharmacist or by the nurse delegated to administer medication in the ward.

A medicine event could be classified in more than one OL category. In classifying medicine events OL for dose, no deviation from the recommended calculated dose was allowed. There are no guidelines that standardise rounding up or down of a calculated dose.[50] The extent of UR and OL medicine use was documented overall and per subspecialty.

Medicines prescribed were categorised according to the WHO ATC classification to the fifth level.[52] This system classifies medicines into different groups according to the organ or system on which their chemical, pharmacological and therapeutic properties are exerted.[52] The medicines are divided into 14 main groups (first level), with one pharmacological/therapeutic subgroup (second level).[52] The third and fourth levels comprise the chemical/pharmacological/therapeutic subgroups, and the fifth level is the chemical substance.[52] Individual medicines were then classified to the fifth level using the WHO ATC classification, and this allowed evaluation of the reasons for OL and UR use of individual medicines.[52]

The patients were classified into four age groups: newborns (0–27 days), infants (28 days to 23 months), children (2–11 years) and adolescents (12–18 years) according to the International Conference on Harmonisation Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population.[53]

2.8 Statistical analysis

Standard descriptive statistics were used. The frequencies of medicine events were calculated using the IBM Statistical Package for Social Sciences (SPSS software, version 19).

2.9 Inclusion and exclusion criteria

2.9.1 Inclusion criteria

All paediatric patients aged 0–18 years admitted to the highly specialised medical care wards (Level 3 care) at Tygerberg Hospital, which included neonates born outside of Tygerberg Hospital and referred for highly specialised paediatric health care at the hospital (Level 3 care).[54]

2.9.2 Exclusion criteria

- All neonates born in Tygerberg Hospital who were admitted to the neonatal critical care unit and neonatal wards.
- All children admitted to the paediatric intensive care unit.
- All children admitted for general paediatric health care (Level 2).
- All children attending ambulatory clinics.
- All children attending the paediatric emergency care department.

Chapter 3: Results

3.1 Demographics

There were 211 admissions, but nine patients received no medicines and two patients were excluded due to missing data. For the remaining 199 patients, the male-to-female ratio was 1:1.06 and the mean age was 50 months (range 1 month to 199.5 months; median age 33.6 months).

3.2 Diagnosis

The most common diagnosis was tuberculosis (TB) in 20% (40/199) of admissions, most frequently pulmonary TB (10.6%), followed by TB meningitis (7.5%), miliary TB (1%), congenital TB (1%) and tuberculous granulomas (0.5%) (Figure 3.1). Solid tumours accounted for 6% (12/199) of all admissions, with posterior fossa tumours the most frequent (2.5%), followed by neuroblastoma (1.5%), nephroblastoma (1.5%) and retinoblastoma (0.5%). Seizure disorders also accounted for 6% (12/199) of admissions, with generalised seizure disorders (5%) occurring more frequently than focal seizures (1%). Complicated gastroenteritis also accounted for 6% (12/199) of admissions. The majority of congenital cardiac defects 5.5% (11/199) were cyanotic cardiac lesions (4.5%). The remainder of the admissions were for bronchopneumonia (4%), airway obstruction (4%), neurodevelopmental disorders (4%), benign haematology (3.5%), disorders of the liver, gallbladder and biliary tree (4%), diabetes mellitus (3.5%), leukaemia (3.5%) and autoimmune disorders (3.5%). Chronic lung disease, glomerular disease and gastrointestinal disorders each represented 3% (Figure 3.1). Half of the patients (50%) had HIV and TB coinfection.

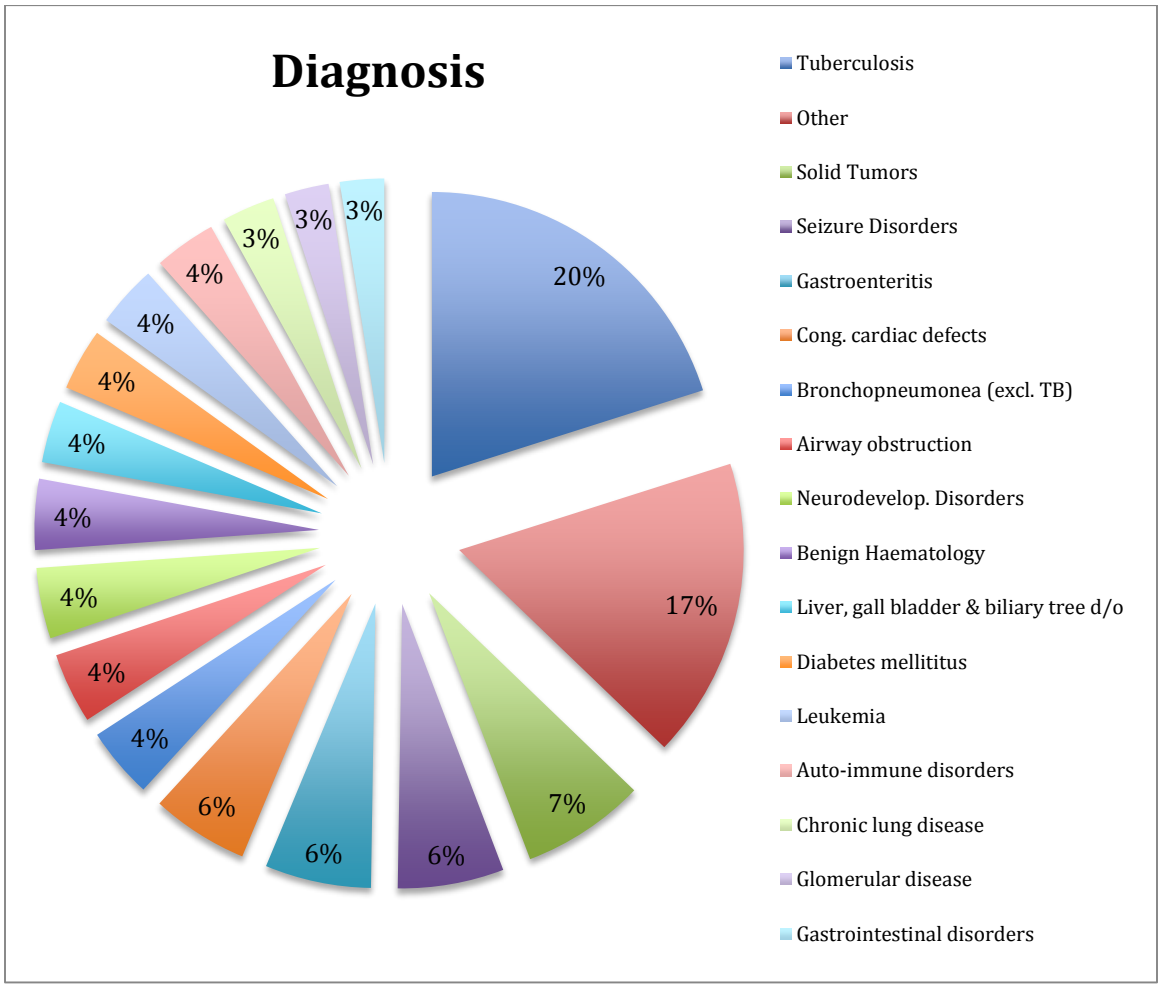

Figure 3.1: Overall diagnosis of patients

In the subcategory 'other', congenital malformations (genito-urinary and respiratory tract) accounted for 2% of admissions, while encephalopathies, diabetes insipidus and cardiac disease (syncope, palpitations and cardiac failure) each was responsible for 1.5% of admissions (Figure 3.2). Benign tumours, idiopathic intracranial hypertension, hydrocephalus, spontaneous bacterial peritonitis, foreign bodies, ambiguous genitalia, kidney disease (acute renal failure and chronic kidney disease) and infections (sepsis and nontuberculous meningitis) each accounted for 1% (2/199) of admissions. Ataxia, dermatophyte infections, pulmonary hypertension, hypoglycaemia and osteogenesis imperfecta each accounted for 0.5% (1/199) of admissions.

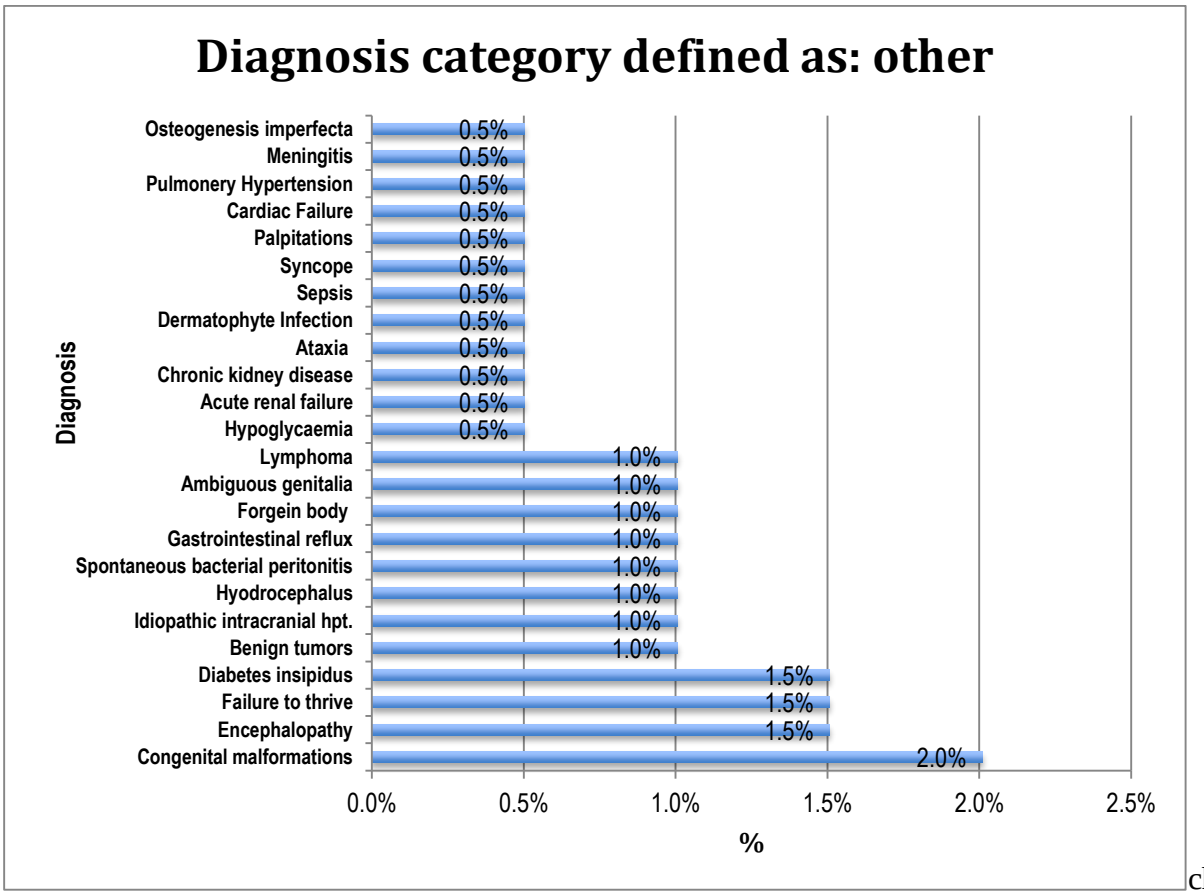

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Figure 3.2: Diagnostic category defined as 'other'

3.3 Anatomical therapeutic chemical classification of medicines, defining extemporaneous use as unregistered use

The 191 different medicines (n) prescribed in 1 507 medicine events were classified into medicine groups according to the WHO ATC classification (appendixes 1 and 2). The therapeutic subclasses (Figure 1) of medicines most frequently prescribed were general anti-infectives for systemic use (39% of medicine events with 49 medicines), medicines acting on the alimentary tact and metabolism (22% of medicine events with 33 medicines), medicines acting on the central nervous system (12% of medicine events with 19 medicines) and systemic hormonal preparations (5% of medicine events with 9 medicines). OL medicine events most prevalent in the subclasses were general anti-infectives for systemic use (15% of medicine events OL, 37 medicines OL), medicines acting on the alimentary tract and metabolism (4.1% of medicine events OL, 17 medicines OL) and medicines acting on the central nervous system (2.4% of medicine events OL, 12 medicines OL). UR medicine events were most frequent in the subclasses general anti-infectives for systemic use (J) (11% of medicine events UR, 12 medicines UR [4 medicines not registered, 9 medicines used extemporaneously]), followed by medicines acting on the alimentary tract and metabolism (A) (3.3% of medicine events UR, 11 medicines UR [3 medicines not registered, 8 medicines used extemporaneously]) and medicines acting on the cardiovascular system (C) (2.5% of medicine events UR, 9 medicines UR [6 medicines not registered, 4 medicines used extemporaneously]).

In all the subclasses, dose was the most common reason for OL use (78% of OL medicine events) except for the systemic hormonal preparations, excluding sex hormones and insulin (H), for which indication (3% of OL medicine events) was the most common reason for OL use. In all the subclasses, extemporaneous medicine compounding was the most common reason for UR use (75% of UR use). In the subclass alimentary tract metabolism (A), mineral supplements (A12) and medicine for acid-related disorders (A02) were most frequently used OL for dose. The medicines most frequently used OL were zinc (32 OL events, 29 OL events for dose) and omeprazole (9 OL events, 6 OL events for dose). In the subclass of medicines acting on the central nervous system (N), psycholeptics (N05) followed by analgesics (N02) were most frequently used OL. Paracetamol was used OL most frequently (11 OL events, 10 OL events for dose), followed by diazepam (7 OL events, 5 OL events for dose). For the subclass antineoplastic and immune-modulating agents (L), the

antineoplastic agent (L01) and cytrabine were most frequently used OL, and the reason for OL use was the lack of paediatric data (Appendix 1).

Table 3.1: WHO ATC classification of medicine, defining extemporaneous use as UR use

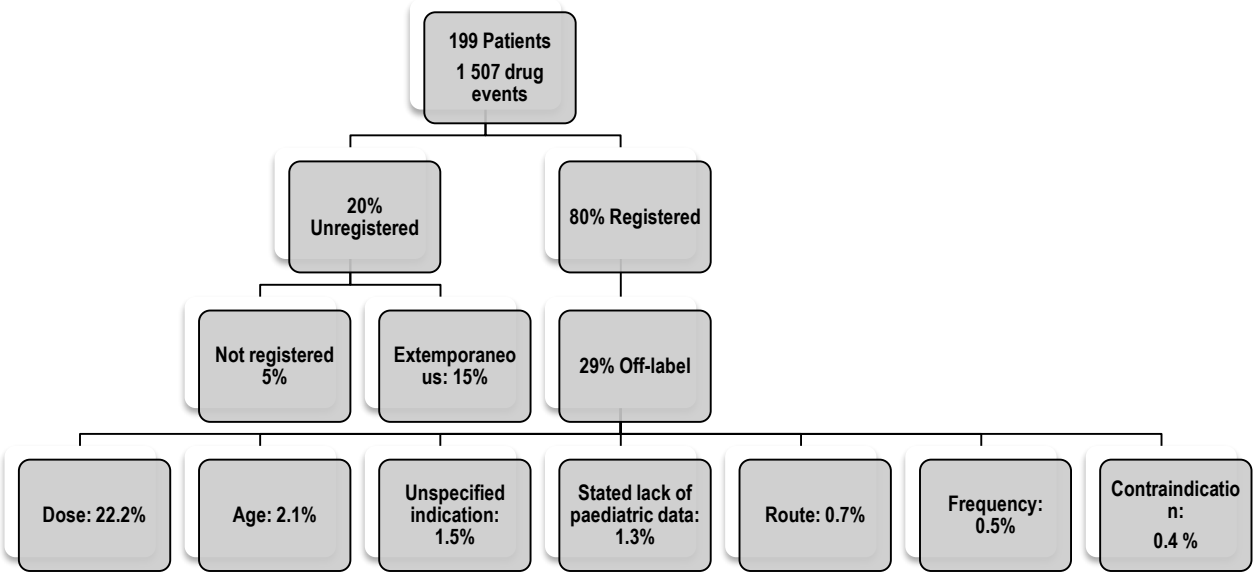
ATC classification	No. of medicines (medicine events %)	No. OL medicines	OL medicine events: n (%)	No. UR medicine
Alimentary tract and metabolism	33 (22%)	17	62 (4.1%)	11
Blood and blood-forming organs	11 (4%)	2	17 (1.1%)	4
Cardiovascular system	11 (4%)	3	12 (0.8%)	9
Dermatologicals	12 (3%)	4	7 (0.5%)	0
Genito-urinary system and sex hormones	2 (0.1%)	1	1 (0.1%)	2
Systemic hormonal preparations (excl. sex hormones and insulin)	9 (5%)	6	27 (1.8%)	2
General anti-infectives for systemic use	49 (39%)	37	226 (15%)	12
Antineoplastic and immune-modulating agents	13 (4%)	5	10 (0.7%)	4
Musculoskeletal system	6 (2%)	3	9 (0.6%)	1
Central nervous system	19 (12%)	12	36 (2.4%)	6
Antiparasitic products	6 (0.9%)	4	6 (0.4%)	0
Respiratory system	11(3%)	6	16 (1.1%)	1
Sensory organs	5 (1%)	2	3 (0.2%)	0
Various	4 (1%)	0	0	2

3.4 Overall medicine events

A total of 1 507 medicine events were prescribed for 199 patients (Figure 3.3a). Each patient had an average of seven medicines prescribed per admission (range 1–28 medicines). Using the definition by Conroy and Turner of extemporaneous use as UR use,[5,35,38] 20% of these medicine events involved UR medicines for paediatric use in South Africa (Figure 3.3a). The majority of UR medicine events were due to extemporaneous compounding (15%), while medicines not registered with the MCC for children accounted for 5% of the medicine events. OL medicine use accounted for 29% of these medicine events, and the most common reasons for OL medicine use were OL use

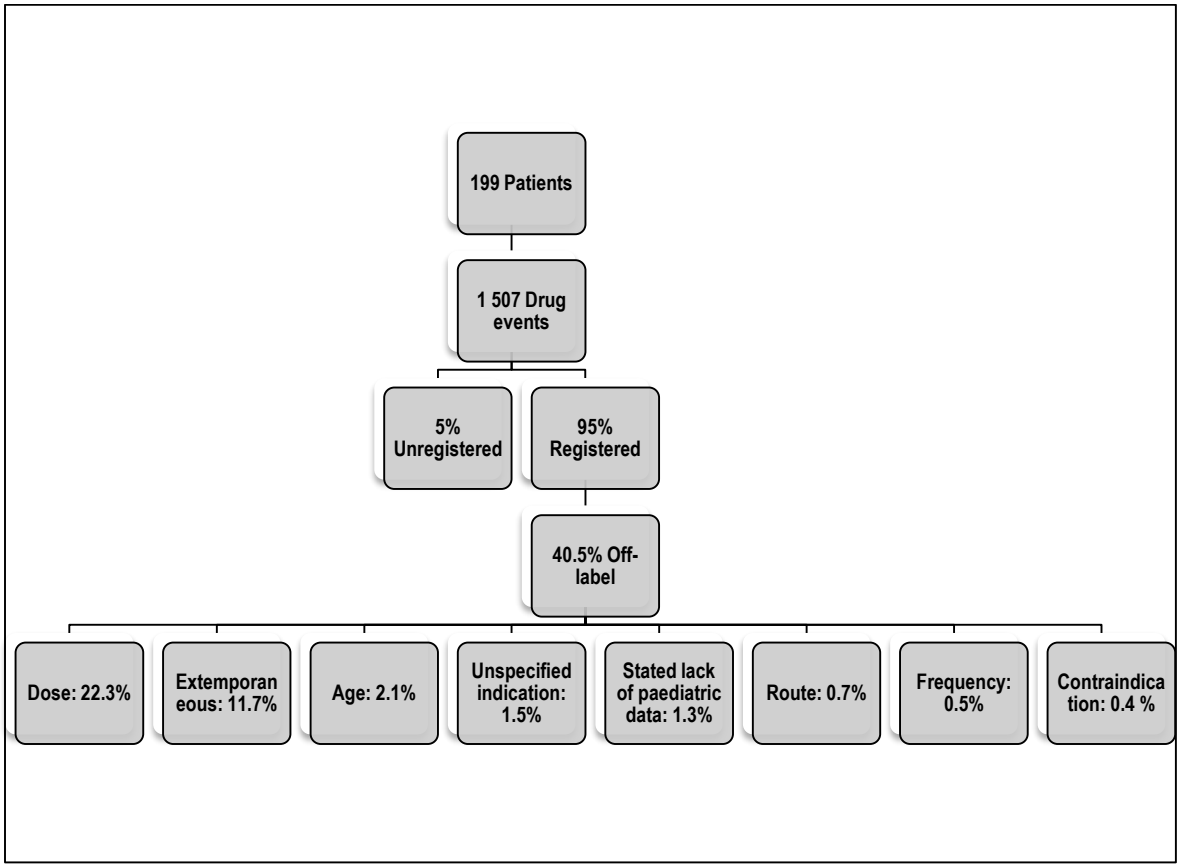
for dose (22%), followed by OL use for age (2%) and OL use for indication (1.5%). OL use for route, frequency and contraindication accounted for less than 1% of medicine events.

Figure 3.3a: Summary of medicine events, defining extemporaneous use as a UR medicine event



If the definitions of the recent Dephi survey are applied, with UR use defined as OL use, only 5% of these medicine events involved UR medicines in South Africa for paediatric use, while OL medicine use increased to 40.5% of these medicine events (Figure 3.3b). The most important reasons for OL medicine use were OL use for dose (22%), followed by OL use for extemporaneous use (12%), OL use for age (2%) and OL use for indication (1.5%). OL use for route, frequency and contraindication accounted for less than 1% of medicine events.

Figure 3.3b: Summary of medicine events, defining extemporaneous use as an OL medicine event



3.5 Medicine events per subspecialty

The number of patients per subspecialty ranged from 4 (rheumatology and immunology) to 44 (neurology). Paediatric pulmonology and haematology-oncology had 38 and 31 patients respectively, followed by 24 for paediatric gastroenterology, 16 for paediatric infectious diseases, 15 for paediatric endocrinology, 14 for paediatric cardiology and 13 for paediatric nephrology. The majority of medicine events occurred in the subspecialty paediatric gastroenterology with 360 medicine events (24 patients) with a range of 1–28, followed by paediatric neurology with 266 medicine events (44 patients) and haematology-oncology with 193 medicine events (31 patients), as well as infectious diseases with 193 medicine events (16 patients) (Table 3.2). Each patient in paediatric infectious diseases received a minimum of 4 medicines, with a range of 4–18 medicines. The average number of medicine events ranged from 3 to 13, with the highest average number of medicines per patient in the subspecialty paediatric infectious diseases (12 medicines per patient) and paediatric gastroenterology (13 medicines per patient).*

Table 3.2: Patient numbers, medicine events, average medicines/patient and range of medicines/patient per subspecialty

Subspecialty	Patient numbers	Medicine events (n)	Average medicines/patient	Range of medicines/patient
Cardiology	14	63	5	1–9
Endocrinology	15	92	6	1–19
Gastroenterology	24	360	***13****	1–28
Infectious diseases	16	193	***12****	4–18
Nephrology	13	94	6	1–19
Neurology	44	266	5	1–22
Oncology and haematology	31	192	6	1–21
Pulmonology	38	232	6	1–19
Rheumatology and immunology	4	15	3	1–7

***** Subspecialties with the highest average number of medicines per patient

Extemporaneous medicine use was the categorical determinant between the two definitions as summarised in Table 3.3, which provides a comparison among the overall results per subspecialty when the different definitions are applied to the dataset. Overall, 15% of all medicine events took place in an extemporaneous manner.

Table 3.3: Summary of overall results per subspecialty, defining extemporaneous use as (a) UR use or (b) OL use

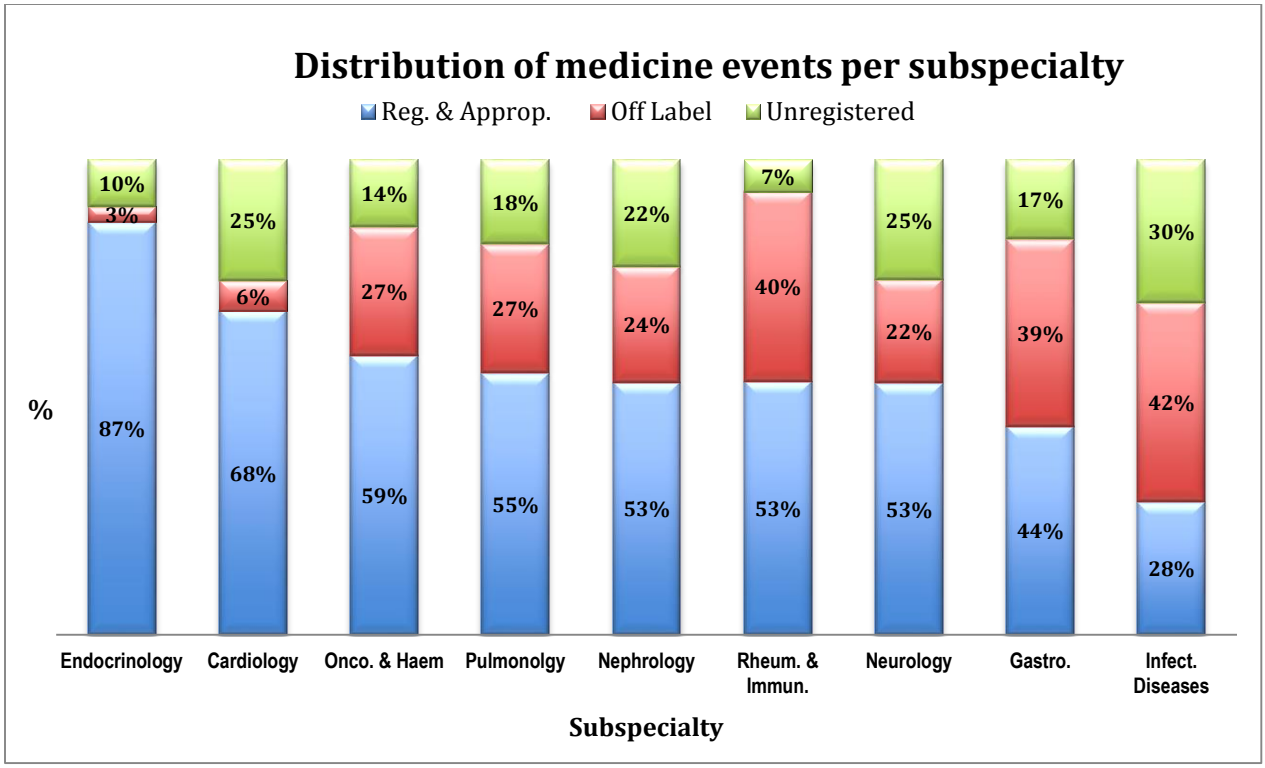
Subspecialty	(a) Medicine events defining extemporaneous use as UR use		(b) Medicine events defining extemporaneous use as OL use	
	UR medicine use	**OL medicine use**	**UR medicine use**	**OL medicine use**
Cardiology	**25%***	6%	3%	32%
Endocrinology	10%	3%	**9%***	3%
Gastroenterology	17%	***39%***	1%	***51%***
Infectious diseases	**30%***	***42%****	6%	***59%****
Nephrology	22%	24%	**15%***	29%
Neurology	**25%***	***22%****	4%	***39%****
Oncology and haematology	**14%**	27%	9%	32%
Pulmonology	18%	***27%***	3%	***41%****
Rheumatology and immunology	***7%***	*40%*	*0%*	*47%*

* Subspecialties with the highest percentage of medicine events UR and OL

UR medicine use was most frequent in infectious diseases (30%), followed by neurology and cardiology with a quarter (25%) of medicine events UR in each specialty (Figure 3.4a) if extemporaneous use is defined as UR.[25,35] Just over one-fifth of medicine events were UR in nephrology (22%), 18% were UR in pulmonology, 17% were UR in gastroenterology and 14% were UR in oncology and haematology. In endocrinology, 10% of medicine events were UR, with only 7% of medicine events UR in rheumatology and immunology. More than one-third of medicine events in infectious diseases (42%), rheumatology and immunology (40%) and gastroenterology (39%) were OL, followed by 27% for the subspecialties pulmonology and haematology-oncology

(Figure 3.4a). In nephrology, nearly a quarter of medicine events were OL (24%), with 22% of the medicine events OL for paediatric neurology, 6% OL for cardiology and 3% OL for endocrinology.

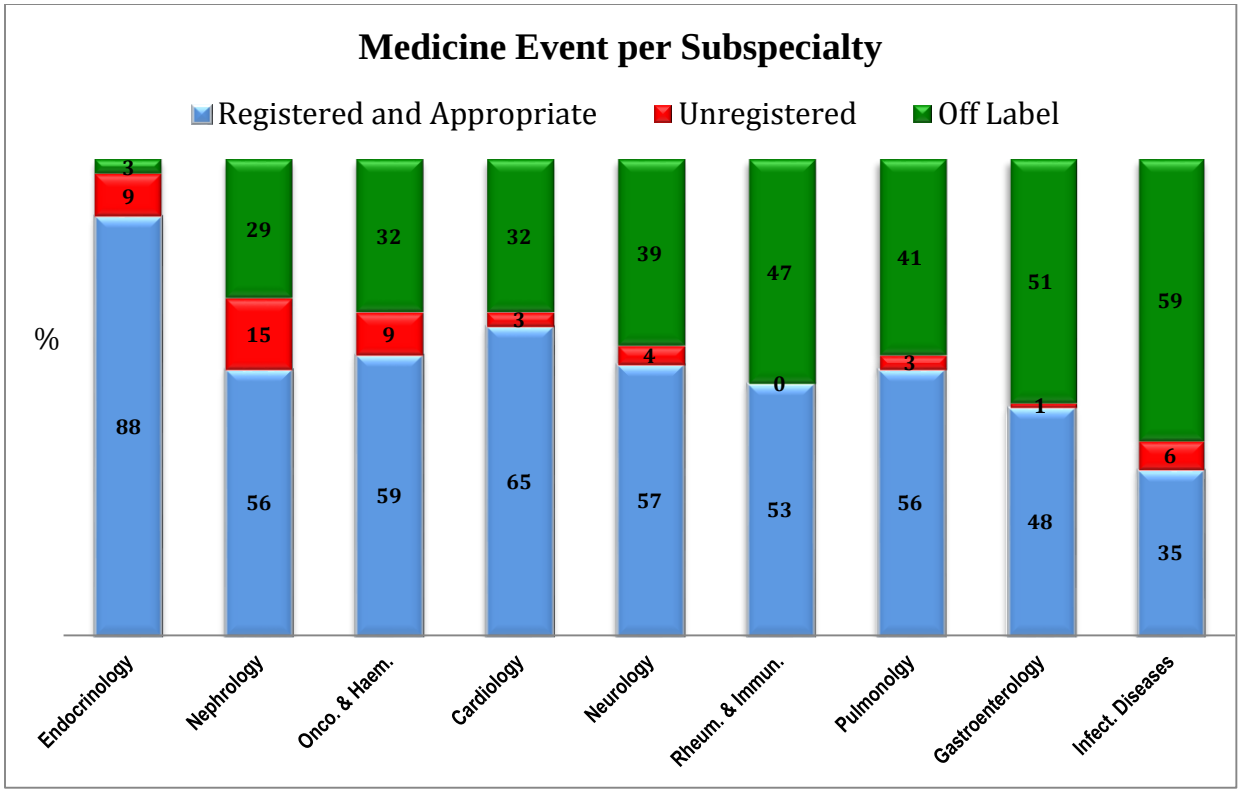
Figure 3.4a: Distribution of medicine events per subspecialty, defining extemporaneous use as UR use



Far lower UR medicine use was found when extemporaneous use was defined as OL use, with the most frequent UR use found in paediatric nephrology (15%), followed by paediatric oncology and haematology (9%) and paediatric endocrinology (9%). The incidence of paediatric infectious diseases UR events decreased to 6%, for paediatric neurology to 4% and for paediatric cardiology and paediatric pulmonology to 3% (Figure 3.4b). More than half the medicine events in paediatric infectious diseases (59%) and paediatric gastroenterology (51%) were OL, followed by paediatric rheumatology and immunology (47%), paediatric pulmonology (41%) and paediatric neurology (39%). In paediatric oncology and paediatric cardiology, 32% of the medicine events were OL in

each of the respective specialties, with 29% OL in paediatric nephrology and 3% OL in paediatric endocrinology (Figure 3.4b).

Figure 3.4b: Distribution of medicine events per subspecialty, defining extemporaneous use as OL use

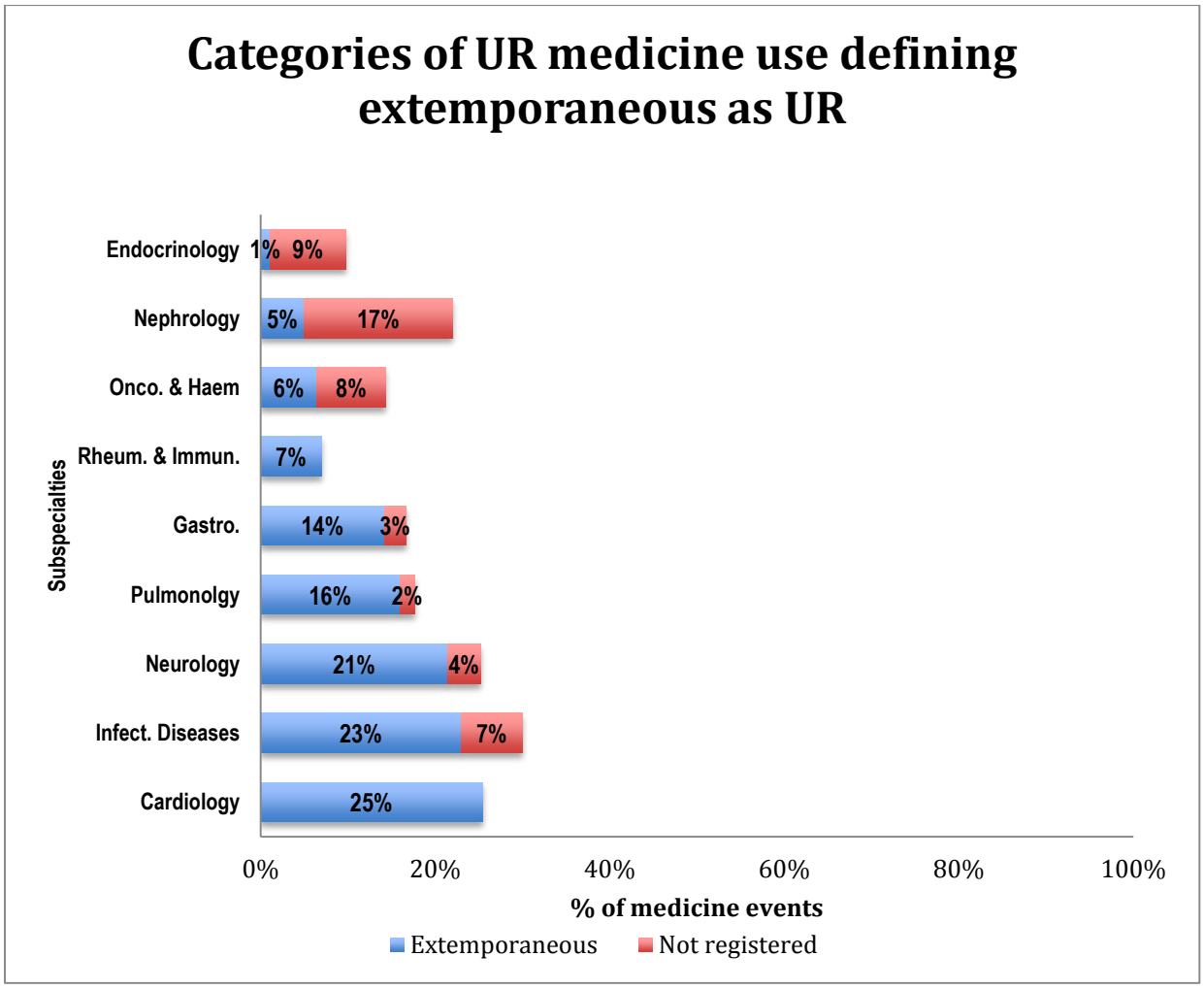


When extemporaneous use was defined as UR use, there were two categories of UR medicine use: medicines not registered with the MCC and extemporaneous medicine use. When this definition was applied, a quarter of medicine events in paediatric cardiology (25%), followed by decreasing frequency for the subspecialties paediatric infectious diseases (23%), paediatric neurology (21%), paediatric pulmonology (16%) and paediatric gastroenterology (14%), were UR for extemporaneous use (Figure 3.5). Less than 10% of medicine events in paediatric rheumatology and immunology

(7%), paediatric oncology and haematology (6%), paediatric nephrology (5%) and paediatric endocrinology (1%) were UR for the category extemporaneous use (Figure 3.5).

Medicine events for medicines not registered with the MCC for paediatric use were most frequent in paediatric nephrology (17%), paediatric endocrinology (9%), paediatric haematology and oncology (8%) and paediatric infectious diseases (7%) (Figure 3.5). Less than 5% of medicine events were UR for medicines not registered with the MCC in paediatric neurology (4%), paediatric gastroenterology (3%) and paediatric pulmonology (2%), with no medicine events UR in paediatric cardiology and paediatric rheumatology and immunology (Figure 3.5).

Figure 3.5: Categorical distribution of UR medicine events per specialty, defining extemporaneous use as UR use



3.6 Off-label medicine event reasons per subspecialty

When OL medicine use was analysed, excluding extemporaneous use as OL use, the most common reason for OL medicine use in the majority of paediatric subspecialties was OL use for dose, followed by frequency and age (Table 3.4a). In paediatric cardiology, the most common reason for OL medicine use was a stated contraindication, accounting for 4.8% of medicine events.

Table 3.4a: Subcategories of OL medicine use per subspecialty, excluding extemporaneous use as OL use

Subspecialty	Reason for OL medicine use (%)

Cardiology	Contraindication (4.8%), indication (1.6%)
Endocrinology	Dose (1.1%), age (1.1%), route (1.18%)
Gastroenterology	Dose (30%), lack of data (3.3%), age (2.8%), route (1.7%), frequency (1.1%), indication (0.6%)
Infectious diseases	Dose (38.3%), age (2.1%), lack of paediatric data (1%), contraindication (0.5%)
Nephrology	Dose (21.3%), indication (3.2%)
Neurology	Dose (19.5%), indication (1.1%), age (0.4%), route (0.4%), frequency (0.4%)
Oncology and haematology	Dose (15%), indication (5.7%), lack of data (2.6%), age (1.6%), contraindication (1%), route (0.5%)
Pulmonology	Dose (19.4%), age (5.6%), frequency (0.9%), route (0.9%), indication (0.4%)
Rheumatology and immunology	Dose (0.3%), indication (0.1%)

When OL medicine use was analysed, including extemporaneous use as OL use, the most common reason for OL medicine use in the majority of paediatric subspecialties was OL use for dose (Table 3.4b). Extemporaneous compounding was the most common reason for OL medicine use in paediatric cardiology (58%), paediatric neurology (53%) and paediatric infectious diseases (35%).

Table 3.4b: Subcategories of OL medicine use per subspecialty, including extemporaneous use as OL use

Subspecialty	**Reasons for OL use**
Cardiology	Extemporaneous use (58%), contraindication (21%), dose (16%), indication (5%)
Endocrinology	Dose (28%), lack of data (28%), extemporaneous use (22%), indication (14%), route (8%)
Gastroenterology	Dose (51%), extemporaneous use (22%), lack of data (15%)
Infectious diseases	Extemporaneous use (35%), lack of data (12%), age (2%), frequency (1%)
Nephrology	Dose (64%), extemporaneous use (18%), indication (13.5%), lack of data (4.5%)
Neurology	Extemporaneous use (53%), dose (32%), lack of data (5%), frequency (4%), indication (3%), route (2%), age (1%)
Oncology and haematology	Dose (60%), indication (21%), extemporaneous use (9%), route (6%), lack of data (4%)
Pulmonology	Dose (45%), extemporaneous use (30%), frequency (10%), age (5.5%), lack of data (5.5%), indication (1%)

3.7 Medicines most frequently prescribed and reasons for off-label and unregistered use

The 11 most commonly prescribed medicines were paracetamol (4.9%), isoniazid (4.6%), zinc (3.5%), prednisone (3.4%), pyrazinamide (2.4%), co-trimoxazole (2.2%), rifampicin (2%), ethambutol (1.9%), ethionamide (1.7%), amikacin (1.6%) and abacavir (1.5%) (Table 3.5.) More than half the medicine events for lamivudine (77%), zinc (62%) and amikacin (58%) were OL, as well as 42% for co-trimoxazole and 40% for isoniazid. When the most frequent medicines prescribed were analysed excluding extemporaneous use as OL use, the most frequent medicine for OL use was zinc (OL for dose 91%), three-quarters of the medicine events for lamivudine (77% for dose) were OL and more than half of the medicine events for amikacin (54% for dose) were OL. Almost an equal percentage of the medicine events for isoniazid (40%) and co-trimoxazole (39%) were OL for dose. Nearly one-third (27%) of the medicine events for prednisone were OL, and the reasons included indication (17%) and age (10%) (Table 3.5).

When the most frequently prescribed medicines were analysed including extemporaneous use as OL use, nearly all the medicine events for the antimycobacterials were OL for extemporaneous use (pyrazinamide 95%, ethambutol 93% and ethionamide 92%). For zinc, 91% of medicine events were still OL for dose, and more than half the medicine events for the systemic anti-infectives (abacavir 67% and amikacin 54%) and 39% for co-trimoxazole were OL for dose (Table 3.5).

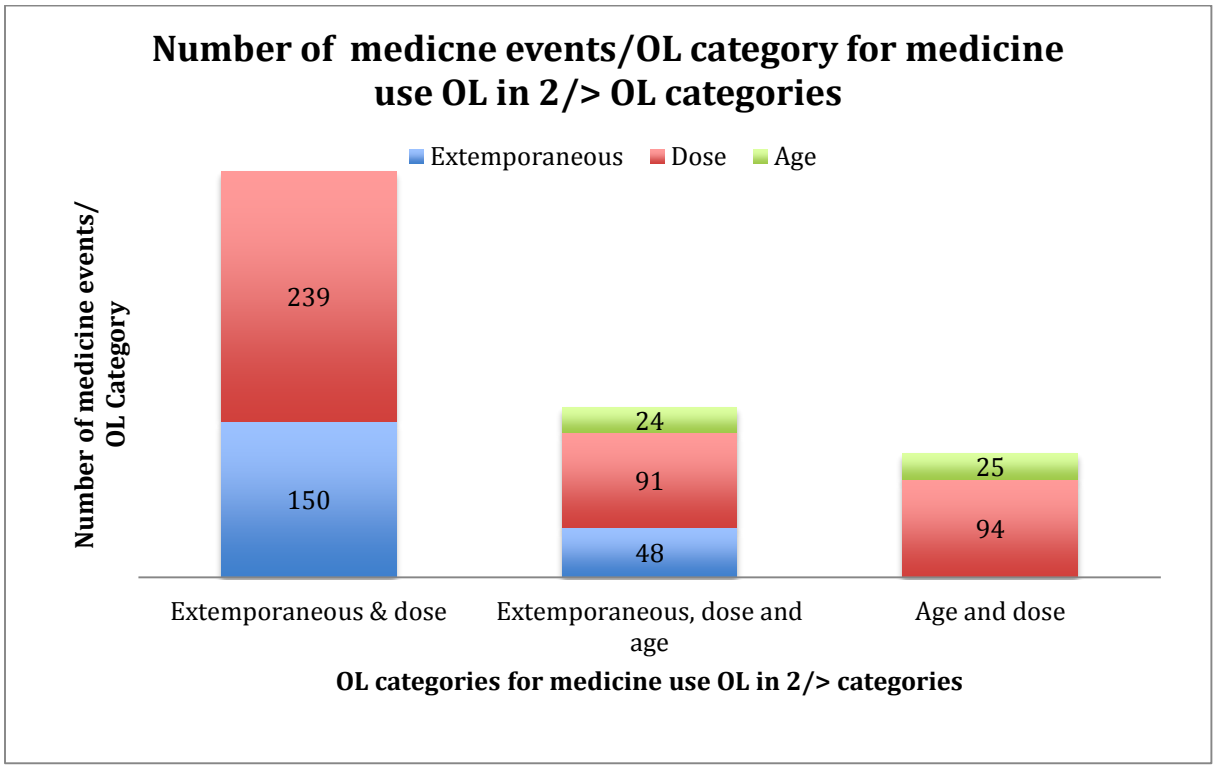
Table 3.5: Summary of the 11 most frequently prescribed medicines and reasons for OL use, excluding (a) and including (b) extemporaneous use as OL use

Medicine	**Medicine events n (%)**	**(a) OL events excluding extemporaneous use**		**(b) OL events including extemporaneous use**	
		OL medicine events n (%)	**Reason for OL use n (%)**	**OL medicine events n (%)**	**Reason for OL use n (%)**
Paracetamol	74 (4.9%)	11 (15%)	Dose (15%)	11 (15%)	Dose (15%)
Isoniazid	53 (4.6%)	21 (40%)	Dose (40%)	53 (4.6%)	**Extemporaneous (92%)**, dose (40%)
Zinc	52 (3.5%)	**32 (62%)**	**Dose (91%)**, indication 6%, data (3%)	32 (62%)	**Dose (91%)**, indication 6%, data (3%)
Prednisone	52 (3.4%)	14 (27%)	Indication (17%), dose (10%)	14 (27%)	Indication (17%), dose (10%)
Pyrazinamide	36 (2.4%)	7 (19.5%)	Dose (14%), age (5.5%)	36 (2.4%)	**Extemporaneous (95%)**, dose (14%), age (5.5%)
Co-trimoxazole	33 (2.2%)	14 (42%)	Dose (39%), indication (3%)	14 (1 %)	Dose (39%), indication (3%)
Rifampicin	31 (2%)	2 (6.5%)	Dose (3.3%), age (3.2%)	2 (6.5%)	Dose (3.3%), age (3.2%)
Ethambutol	29 (1.9%)	2 (7%)	Dose (3.5%), age (3.5%)	29 (100%)	**Extemporaneous (93%)**, dose (3.5%), age (3.5%)
Ethionamide	26 (1.7%)	2 (8%)	Dose (4%), age (4%)	26 (100%)	**Extemporaneous (92%)**, dose (4%), age (4%)
Lamivudine	26 (1.7%)	**20 (77%)**	**Dose (77%)**	20 (77%)	**Dose (77%)**
Amikacin	24 (1.6%)	**14 (58%)**	**Dose (54%)**, indication (4%)	14 (58%)	**Dose (54%)**, indication (4%)

3.8 Off-label medicine use in two or more categories

A total of 69 patients in 31% of medicine events (n = 446) were exposed to OL medicine use in 2 or more categories. The most frequent combination was for extemporaneous use and dose in 26% (n = 389) of medicine events in 56 patients. OL use for the combination of extemporaneous use, dose and age accounted for 11% of medicine events (n = 163) in 19 patients, while the combination of OL use for dose and age occurred in 8% of medicine events (n = 119) in 19 patients (Figure 3.6).

Figure 3.6: Number of medicine events per OL category for OL medicine use in two or more categories



Younger children were more likely to have an OL medicine event in two different categories, with the frequency of this decreasing with increasing age. The age group neonates had the largest number of OL medicine events for two different categories (3.5%), followed by infants (3%), children (2.7%) and adolescents (0.5%). In HIV-infected patients, 2.7% of medicine events (n = 292) were OL for more than two categories.

3.9 Unregistered medicine use

UR medicine, including extemporaneous compounding, was the main reason for UR medicine use for antimycobacterials, used in the treatment of TB. The five most frequently used UR medicines were potassium chloride (100% UR), ethionamide (96% UR), ethambutol (96% UR), pyrazinamide (94% UR) and isoniazid (92% UR) (Table 3.6a). All were UR because of extemporaneous compounding.

Table 3.6a: Most frequently used UR medicines (including extemporaneous use) and reasons for UR use

Medicine	**Medicine events n (%)**	**UR medicine events n (%)**	**Reason for UR use**
Potassium chloride	16 (1.1%)	16 (100%)	Extemporaneous
Ethionamide	25 (1.5%)	24 (96%)	Extemporaneous
Ethambutol	28 (1.9%)	27 (1.8%)	Extemporaneous
Pyrazinamide	36 (2.4%)	34 (96%)	Extemporaneous
Isoniazid	53 (3.5%)	49 (92%)	Extemporaneous

The most frequently used UR medicines, excluding extemporaneous use, were ofloxacin, ritonavir, amlodipine, clonidine and atenolol (Table 3.6b).

Table 3.6b: Most frequently used UR medicines (excluding extemporaneous use) and reasons for UR use

Medicine	Medicine events n (%)	UR medicine events n (%)	Reason for UR use
Ofloxacin	15 (1%)	15 (100%)	Not registered with the MCC
Ritonavir	8 (0.5%)	8 (100%)	Not registered with the MCC
Amlodipine	7 (0.5%)	7 (100%)	Not registered with the MCC
Clonidine	7 (0.5%)	7 (100%)	Not registered with the MCC
Atenolol	5 (0.3%)	5 (100%)	Not registered with the MCC

3.10 Extemporaneously compounded medicines

The extemporaneously compounded medicines manufactured at the Tygerberg Hospital pharmacy are manufactured based on pharmacopoeias, historical recipes and good pharmaceutical practice. The most frequently prescribed medicines used extemporaneously were essential antimycobacterials, as mentioned above, used in the treatment of TB. More than three-quarters (77%) of medicine events for isoniazid, pyrazinamide, ethambutol and ethionamide and 15% of medicine events for rifampicin were extemporaneous. Other extemporaneously compounded medicines included elemental supplements such as magnesium chloride, potassium chloride and potassium phosphate (62–100% UR), cardiac medicines such as spironolactone (100% UR) and the painkiller morphine (75% UR).

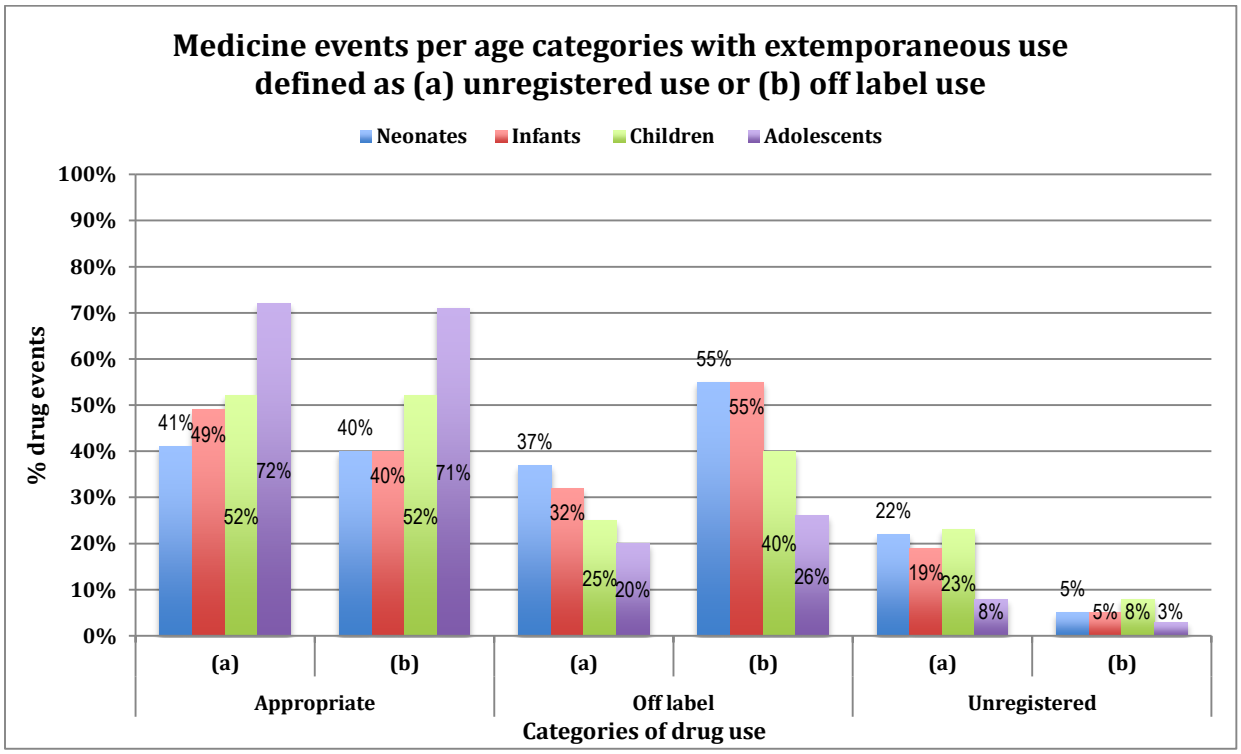
Table 3.7: Most frequently used extemporaneously compounded medicines

Extemporaneously compounded medicines			
Medicine	**Medicine events (n)**	**UR extemporaneous (n)**	**% of medicine events UR**
Isoniazid	53	49	92%
Pyrazinamide	36	28	77%
Ethambutol	28	25	90%
Ethionamide	25	22	88%
Spironalactone	16	16	100%
Potassium chloride	16	16	100%
Potassium phosphate	11	11	100%
Morphine	8	6	75%
Magnesium chloride	8	5	62%
Rifampicin	31	5	16%

3.11 Medicine events per age categories

Medicine events were analysed by age categories.[53] The majority of medicine events (n = 1 507) were for infants (44%; n = 665), followed by children (42%; n = 640), adolescents (8%; n = 116) and neonates (6%; n = 86). UR medicine events, including extemporaneous use, were most frequent in children (23%), followed by neonates (22%), infants and toddlers (19%) and adolescents (8%) and decreased to 8% for children, 5% for neonates, 3% for infants and toddlers and 3% for adolescents if extemporaneous use was defined as OL. OL medicine events (including extemporaneous use) were equally frequent in neonates and infants (55% each), followed by children (40%) and adolescents (26%) (Figure 3.7).Younger paediatric patients were therefore more likely to be exposed to an OL medicine event as well as an OL or a UR medicine event, while appropriate medicine use was most frequent in adolescents and children (Figure 3.7).

Figure 3.7: Medicine events per age categories, defining extemporaneous use as (a) UR use or (b) OL use



Irrespective of whether OL medicine use included or excluded extemporaneous use, OL medicine use for dose was the most common reason for OL use across all age groups. More than a quarter of

medicine events in the age groups neonates (26.7%) and children (25.7%) and just over a fifth in the age group children (20.5%) were OL. When extemporaneous use was defined as OL use, it was the second most common reason for OL use in children (16.2% of medicine events) and infants (17.4% of medicine events OL for extemporaneous use) (Table 3.8).

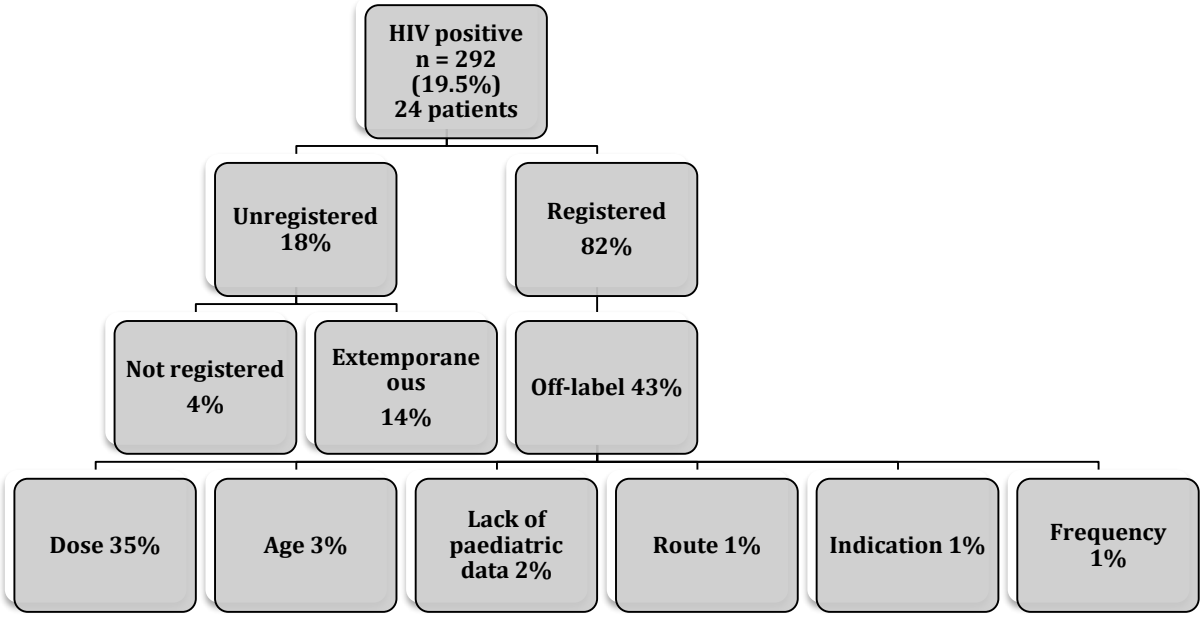
Table 3.8: Reasons for OL medicine use by age categories

	Neonates	Infants	Children	Adolescents
Dose	26.7%	25.4%	20.5%	10.3%
Extemporaneous	17.4%	16.2%	14.8%	6.0%
Age	5.8%	2.6%	1.6%	0.0%
Lack of paediatric data	1.2%	1.5%	1.1%	0.9%
Route	1.2%	0.9%	0.5%	0.9%
Frequency	1.2%	0.6%	0.2%	0.9%
Indication	0.0%	0.8%	1.6%	6.0%
Contraindication	1.2%	0.5%	0.2%	0.9%

3.12 Off-label and unregistered medicine events in HIV-infected patients

Of the 199 patients, 24 were HIV infected, 167 were HIV negative and 8 were HIV exposed but uninfected. There were 292 medicine events in the 24 HIV-infected patients, which accounted for 19.2% of the overall number of medicine events. These patients received 18% UR medicines (if extemporaneous use was included as UR) and 43% OL medicines. The most common reason for UR use was extemporaneous compounding (14%), followed by medicines not registered with the MCC (4%). The most common reasons were OL use for dose (35%), age (3%) and lack of paediatric data (2%). OL medicine use occurred in two different categories in 2.7% of these medicine events.

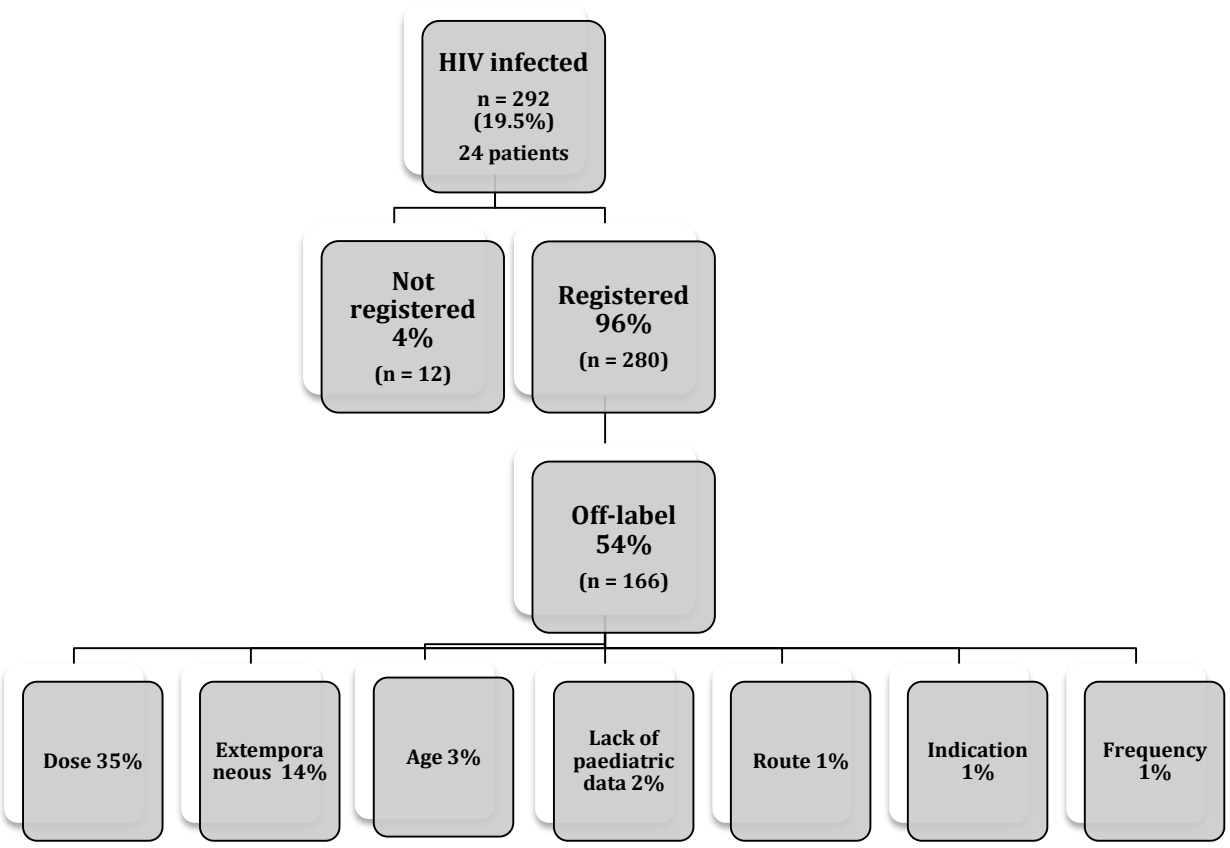
Figure 3.8a: UR and OL medicine use in HIV-infected patients, defining extemporaneous use as UR use



Of the 292 medicine events occurring in the HIV-infected patients, 4% were UR and 54% were OL (including extemporaneous use as OL use). The most common reasons were OL use for dose (35%), extemporaneous use (14%) and age (3%). OL use for lack of paediatric data accounted for 2% and route, indication and frequency accounted for 1% of medicine events each. OL medicine use

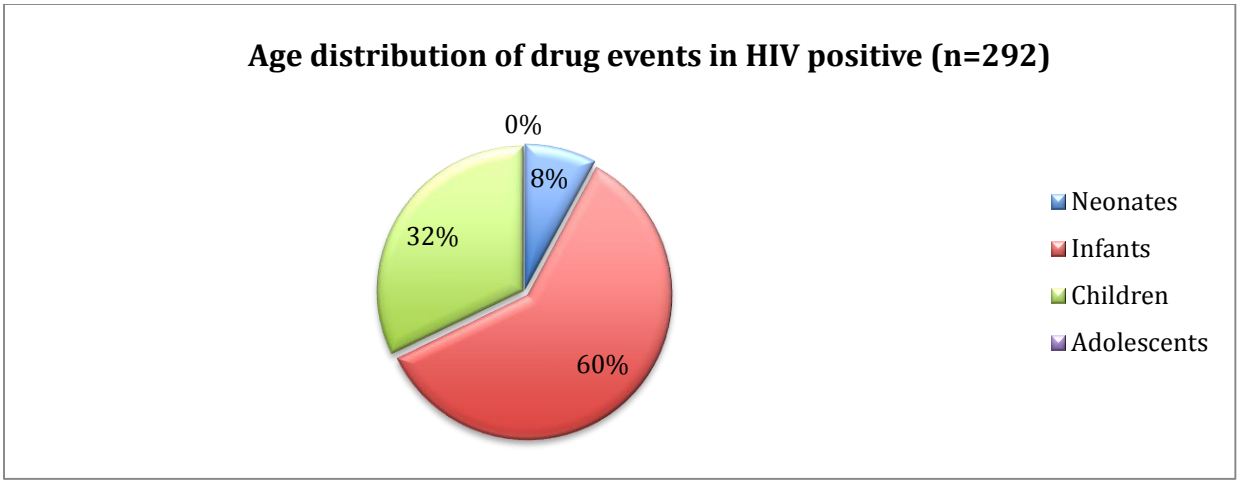
occurred in two different categories in 2.7% of these medicine events. OL medicine use for more than two categories most frequently occurred for extemporaneous use (1.7%) and indication.

Figure 3.8b: UR and OL medicine use in HIV-infected patients, defining extemporaneous use as OL use



The 24 HIV-infected patients were distributed over 5 specialties (paediatric infectious diseases – 10 patients, paediatric gastroenterology – 9 patients, paediatric pulmonology – 3 patients and paediatric nephrology and neurology – 1 patient each). More than half the medicine events in HIV-positive children were in the age group infants (60%), followed by 32% in children and 8% in neonates. There were no HIV-postive adolescents (Figure 3.9).

Figure 3.9: Age distribution of medicine events in HIV-positive children



Nearly all the HIV-infected patients received highly active antiretroviral therapy (HAART) (23 patients), except one patient in paediatric neurology for whom HAART had not yet been initiated. TB coinfection was present in 50% of the HIV-infected children (Table 3.9).

Table 3.9: Distribution of HIV-infected patients on HAART and TB treatment

The most commonly prescribed medicines (Table 3.10) in HIV-positive patients were co-trimoxazole (6.5%), lamivudine (5.8%), lopinavir/ritonavir (5.5%), abacavir (5.1%) and multivitamin (4.5%). In all the medicines, except multivitamin, the reason for OL use was dose.

Subspecialty	No. of HIV-infected patients on HAART	No. of patients on TB treatment
Infectious diseases	10	4
Gastroenterology	9	5
Pulmonology	3	2
Nephrology	1	0
Neurology	1 (not on HAART)	1 (TBM)

When the most frequent medicines prescribed were analysed, excluding extemporaneous use as OL use, medicine used OL for dose was the most common reason for OL medicine use. More than 80% of medicine events for each of the antiretrovirals used in the treatment of HIV were OL for dose (abacavir 86% OL, lamivudine 82% OL and lopinavir/ritonavir 80% OL), while 42% of the medicine events for co-trimoxazole were OL for dose. More than half the medicine events for zinc were OL (67%), with OL use for dose accounting for 50% of the OL events.

Medicine	**Medicine events n (% of medicine events)**	**(a) OL events excluding extemporaneous as OL**		**(b) OL events including extemporaneous as OL**	
		OL medicine events n (%)	**Reason for OL use**	**OL medicine events n (%)**	**Reason for OL use**
Co-trimoxazole	19 (6.5%)	8 (42%)	Dose	8 (42%)	Dose
Lamivudine	17 (5.8%)	14 (82%)	Dose	14 (82%)	Dose
Lopinavir/ritonavir	16 (5.5%)	13 (80%)	Dose	13 (80%)	Dose
Abacavir	15 (5.1%)	13 (86%)	Dose	13 (86%)	Dose
Multivitamin	13 (4.5%)				
Isoniazid	12 (4.1%)			12 (100%)	Extemporaneous
Zinc	12 (4.1%)	8 (67%)	Dose (50%) Indication (17%)	8 (67%)	Dose
Ritonavir	10 (3.4%)				

Ethambutol	9 (3.1%)			8 (89%)	Extemporaneous

Table 3.10: The 10 most commonly prescribed medicines in HIV-infected patients and reasons for OL use

When medicine events in HIV-infected patients were analysed for their registration status, with extemporaneous use defined as UR use, the most common UR medicines prescribed in HIV-positive patients (Table 3.11) were isoniazid (4.1%), ritonavir (3.4%), ethambutol (2.7%), potassium chloride (1.4%) and pyrazinamide (1%). The reason for UR use was extemporaneous use in all the medicines, except ritonavir, which was not registered in South Africa.

When the most frequent medicines prescribed in HIV-infected patients were analysed, with extemporaneous use defined as OL use, all the medicine events (100%) for the antimycobaterial isoniazid and 89% of the medicine events for ethambutol were OL for extemporaneous use. OL use for dose of the antiretrovirals ranged from 80% (lopinavir/ritvonvir) to 86% (abacavir). When extemporaneous used was defined as UR, more than 80% of the medicine events for the antivirals used to treat HIV infection (abacavir, lopinovir-ritonovir and lamivudine) and 42% of the medicine events for co-trimoxazole were OL for dose.

Medicine	**Medicine events n (%)**	**(a) UR events including extemporaneous use**		**(b) UR events excluding extemporaneous use**	
		UR medicine events n (%)	**Reason for UR use**	**UR medicine events n (%)**	**Reason for UR use**
Isoniazid	12 (4.1%)	12 (100%)	Extemporaneous		
Ritonavir	10 (3.4%)	10 (100%)	Not registered	10 (100%)	Not registered with the MCC
Ethambutol	9 (3.1%)	8 (89%)	Extemporaneous		
Potassium chloride	4 (1.4%)	4 (100%)	Extemporaneous		
Pyrazinamide	12 (4.1%)	3 (25%)	Extemporaneous		

Table 3.11: The five most frequently used UR medicines in HIV-infected patients and reasons for UR use

Chapter 4: Discussion of the results

4.1 Discussion

OL and UR medicine use in paediatrics is widespread globally, which was also demonstrated in this study with nearly half (49%) of medicine events being either OL or UR.[7,8,9] UR medicine use in this study accounted for 20% of medicine events, with the majority of UR use due to extemporaneous compounding (15%), using the definition by Conroy et al and Turner et al, which is comparable to another study from Nigeria (20.4%) but higher than in Brazil (5.5%) and Palestine (7.1%) as other low- and middle-income countries.[5,6,13,34,41] However, exposure to UR medicine events for the paediatric population in the current study was higher when compared to high-income countries such as Australia (2.6%), Germany (0.4%) and the Netherlands (14%).[12,32,35] Extemporaneous medicine compounding was the most common reason for UR medicine events with a frequency of 10% in Finland, which is similar to this study with 15% extemporaneous use.[30]

OL medicine use was high in India, a low-income country, with more than half of the medicine prescriptions (50.6%)[27] being OL, while high-income countries reported OL medicine use ranging from 20% in the UK to 31%[4] in the USA.[27,26,4] The reported range of OL medicine use in middle-income countries was 21.5–39.5%, which is comparable to the frequency of OL medicine use in this study (29%).[13,41] The most common reason for OL medicine use was dose (29%), which is comparable to a study from Finland (22%) but higher than in the UK (8%) and lower than in Australia (47.4%).[4,26,32] Although dose was the most common reason for OL medicine use in both Germany and Finland, the second most common reason was lack of paediatric data, which differs from the current study in which OL use due to lack of paediatric data was particularly uncommon.[4,12] OL medication use for age (2.1%) was also far lower than in studies from Brazil (7.9%), Finland (9.8%) and the UK (9.8%).[13,4,26]

Overall, the medicines most frequently used in the majority of studies were anti-infectives for systemic use, respiratory medicines, medicines acting on the central nervous system and alimentary tract medicines.[29,32] Only two studies utilised the WHO ATC classification methodology to classify medicines.[29,32] Direct comparison could therefore be made with the studies that utilised the ATC

classification.[29,32] In this study, the most frequent ATC categories prescribed were anti-infectives (J) for systemic use (39%), alimentary tract medicines (A) (22%) and medicines acting on the central (N) nervous system (12%). Similar ATC categories were used in Australia, but the frequency of use differed with medicines acting on the central nervous system most frequently used (39%), followed by alimentary tract medicines (15.4%) and anti-infectives (15.1%).[32] The study from Malta found medicines acting on the respiratory system most frequently used (40%), followed by anti-infectives (23%) and central nervous system medicines (13%).[29] The categories with the highest OL medicine events in the current study were anti-infectives (15% OL), alimentary tract medicines (4% OL) and central nervous system medicines (2.4% OL), while UR medicine events were most frequent for anti-infectives (11% UR), alimentary tract medicines (3.3% UR) and cardiovascular medicines (2.5% UR). The OL use differed from studies reported from Malta (59%) and Australia (39%), with both showing more frequent OL use of respiratory medicines,[23,29] followed by central nervous system medicines (55% for Malta; 40.6% for Australia), anti-infectives (52% for Malta) and systemic hormonal preparations (36% for Australia).[29,32]

There was, however, a higher average of seven medicines per patient in the current study (range 0–28 medicine events/patient) than in other studies with an average of 2–4 medicines per patient.[7,8,9] The higher average and range of medicines per patient are probably due to the high prevalence of TB and HIV coinfection Southern Africa.[55] HIV and TB are the leading infectious causes of death worldwide, with 80% of global HIV and TB infection occurring in Southern Africa.[55,56] The Western Cape, the study region, is known to have a particularly high rate of TB, and the prevalence is estimated to be 944/100 000 adult population.[55,57] The actual incidence of childhood TB is unknown, but the WHO estimates that there are 530 000 TB cases in children < 15 years (WHO national guidelines).[57] In South Africa, 20% of TB cases are estimated to occur in children, with a prevalence of 511/100 000 in children < 5 years in the Western Cape.[58] Worldwide, children account for 10% of new HIV infections.[56] Continued transmission and a 4–5-fold rise in the incidence of TB with HIV coinfection have resulted in a dual epidemic.[55] HIV coinfection alters the pathogenesis of TB, increasing the risk of developing active TB (from latent or new infections).[56] More disturbing is the fact that South Africa also has a high burden of multimedicine-resistant and extremely medicine-resistant TB. Dual therapy is often necessary with antimycobacterials and HAART.[56,57]

The TB and HIV coinfection rate in this survey was 50%, which correlates with worldwide statistics.[56] The participants who were HIV and TB coinfected formed a highly selected patient group in the study. In the subclass antimycobacterials (J04), extemporaneous compounding was the most common reason for UR use, and in the subclass antivirals for systemic use (J05), the most common reason for OL medicine use was dose, using the definition by Conroy and Turner.[5,6] Extemporaneous compounding (14%) also accounted for the majority of UR medicine events (18%) in the HIV-infected patients. The majority of the most commonly prescribed extemporaneously prepared medicines were therefore isoniazid, pyrazinamide, ethambutol, ethionamide and abacavir. For the medicine subclass of antimycobacterials (isoniazid, pyrazinamide, ethambutol and ethionamide), no information on extemporaneous medicine compounding is available in the South African package insert, the MIMS reference or the South African Medicines Formulary and therefore these medicines are UR.[27,50,51]

The extent of extemporaneous compounding (67%) in the subclass antimycobacterials highlights the lack of child-friendly formulations. Clinical dosing of TB medicines takes place by weight-banded dosing charts, with recommended dosing ranges derived by the WHO.[57] The weight-banded charts are derived from a medicine dosing range and supported by pharmacokinetic studies.[57] Although the weight-banded dosing results in higher serum medicine levels for children aged less than two years, this is necessary to produce effective bactericidal activity.[57] Systemic reviews have reinforced the safety profile of weight-banded dosing by providing evidence of no risk of increased toxicity, especially hepatotoxicity due to pyrazinamide or isoniazid use or optic neuritis due to ethambutol use.[57] Weight-banded dosing charts are used as a standard of clinical care in treatment of childhood TB and provide dosing guidance to clinicians with respect to tablets that are scored and manipulation of antimycobacterials tablets so that the therapeutic needs of paediatric patients are met.

Pharmaceutical justification for extemporaneous compounding is the absence of an equivalent registered medicine formulation,[5,25,27,35,38] making extemporaneous compounding justifiable in certain situations. With respect to orphan and rare diseases, registered formulations or viable alternatives may not meet the special therapeutic needs of treatment.[27] It may also not be profitable

for pharmaceutical companies to manufacture and distribute a medicine.[59] The available formulations and strengths of a medicine may be limited, and in the presence of allergies to specific ingredients in a medicine, extemporaneous compounding may be necessary, as demonstrated for the anti-TB medicines in this study.[27] The risks associated with extemporaneous medicine use are formulation failure due to medicine degradation, excipients and medicine binding, and the use of inadequately validated and historical formulas.[27] Microbial contamination during manufacturing or growth and by-products of microbial degradation in the particular medicine can lead to spoilage.[27] This is also a risk factor for infection, especially for immunocompromised patients.[27] Calculation errors can occur during manufacturing and medicine administration.[27] Ingredients and excipients should be physiologically age appropriate and religiously acceptable and should not precipitate systemic or local adverse reactions. Health, safety and quality assurance should be maintained during manufacturing, storing and administering the medicine.[27,59]

The majority of medicine events for antiretroviral medicines were OL for dose when compared to the South African manufacturers package insert and the South African Medicines Formulary but correlated well when compared to the standardised weight-banded dosing charts used in clinical practice.[60] The clinical dosing of HAART is guided by weight-banded paediatric dosing charts compiled by the Child and Adolescent Committee of the HIV Clinicians Society in collaboration with the National Department of Health.[60] Weight-banded dosing charts were developed by the WHO paediatric ARV working group using scientific data and pharmacokinetic models.[61] There are target doses for ARVs that are targeted within the specific weight band.[61] The optimal dose within a weight band was based upon manufacturers' information, ARV formulation choices, clinical studies and expert paediatric pharmacology consultation.[61] Dosing within a particular weight band may be above or below that recommended by the manufacturer.[61] Derived doses on the weight bands avoid dosing a medicine below 90% or above 125% of the target dose.[61] For the antiretroviral medicines, 68% of the medicine events were OL for dose when compared to the reference sources but correlated with the weight-banded dosing charts used in clinical practice. Weight-banded dosing charts for HIV and TB therapy are scientifically derived and clinically useful; clinicians should seek the MCC's approval to add these weight-banded charts to package inserts and pharmacological resources. Ritonavir was the only ARV not registered in South Africa, although pharmacokinetic data is

available for infants and children, especially used to boost other protease inhibitors in combination with TB therapy.[61] Stavudine was the only antiretroviral medicine used in an extemporaneous manner.[61]

Individual medicines worth mentioning are paracetamol and captopril. Paracetamol was listed as the most frequently used medicine in seven studies with a medicine event frequency ranging from 5% to 18.3% and with OL medicine events for the medicine ranging from 4% to 52%.[4,13,26,35,41] Paracetamol was prescribed in 4.7% of medicine events in this study, with an OL medicine event rate of 15%, which was similar to findings from a study in Nigeria.[41] With 15% of the medicine events being extemporaneous, all the medicine events for the antihypertensive captopril were not registered, with Croatia, Brazil, Germany and Palestine also reporting similarly.[10,12,13,34]

For the subspecialties paediatric neurology and paediatric endocrinology, all the OL and UR medicine events were higher, while in paediatric endocrinology, UR medicine events were higher and OL events lower when compared to a similar study in Croatia.[10] The frequency of OL medicine events in the subspecialty paediatric pulmonology was 27%, which is comparable to the results reported by Schmiedl et al, with 29.8% of medicine events being OL, but lower than in Malaysia (35.6%).[62] The most common reason for OL use was dose, which differed from Malaysia and Germany where it was indication. The subclass of medicine used most frequently OL was to treat obstructive airway disease, which was comparable to Germany and Malaysia.[62,63]

In paediatric oncology with 27% OL use, with the most common reason being dose (15%), the finding was similar to the findings reported by Conroy et al (26%) and Van Den Berg et al (21%).[49,64] UR medicine use was similar to that found by the studies by Conroy et al (19%) and Paveveski (18%).[49,55,10] The most common reason was dose, similar to a report by Van den Berg et al.[64] The reason for UR medicine use for antineoplastic medicines was medicines not registered with the MCC (17%), while Conroy reported the UR reason as extemporaneous use (16%).[49]

OL medicine use in paediatric gastroenterology in this survey at 39% was similar to that in paediatric gastroenterology units in the UK (37%) but higher in comparison to a similar study in Croatia (10.8%).[10,65] UR medicine events (17%) in paediatric gastroenterology were higher when compared

to reports from the UK (12%) and Croatia (2.7%).[10,65] A possible reason for the higher rates may be the increased frequency of extemporaneous use of medicines in this study population (14%).

In paediatric cardiology, 6% of medicine events were OL and 25% were UR. OL medicine events were lower and UR medicine events were higher in this survey compared to that by Bajcetic et al[66] in which 47% of medicine events were OL and 11% were UR. The most common reason for OL use in this study was contraindication, followed by dose and lastly unspecified indication, which differed from the results of Bajcetic et al[66] with the most common reasons for OL use being dose and age.[66] Extemporaneous compounding of spironolactone was common in both studies but occurred at a higher frequency in this study (100%) compared to the study by Bajcetic et al (43%).[66]

4.2 Limitations of the study

The study was conducted in a tertiary health care setting (highly specialised paediatrics) where children with complex pathology were admitted. The results may therefore not be generalisable to the general paediatric population as the severity of disease may differ from children managed in secondary level health care facilities or in ambulatory paediatric clinics, therefore rendering the medicines utilised highly context specific. The medicine events in the age group neonates (0–27 days) may be underrepresented as these children are mostly admitted to neonatal wards, which were not included in this study. The results may therefore not be generalisable to the neonatal population. Medicine manipulation at the point of care/administration is possibly underrepresented since we did not directly observe dispensing/manipulation practices at the point of medicine administration by the dispensing nurse. We only recorded medicines that were known to be extemporaneously compounded in the hospital pharmacy. There are also no clinical guidelines to guide manipulation at the point of medicine administration, which are important to develop. Extemporaneous manipulation is done at the dispensing health staff's discretion and is highly dependent on the clinical context in which medicine is being utilised; this further makes the generalisability of these results difficult. The odds of an adverse medicine reaction in relation to OL or UR medicine utilisation or the number of medicines prescribed cannot be commented on as this was not part of the aims and objectives of the study. The study duration of three consecutive months may not have been sufficient

for data collection in a highly selected population with complex and sometimes rare and orphan diseases that require subspecialist care.

4.3 Conclusions and recommendations

OL medicine use (29%) and UR medicine use (20%) were common in highly specialised paediatric inpatient care at Tygerberg Hospital in Cape Town. The most common reasons for OL use were dose (22%) and age (2.1%), while extemporaneous compounding (15%) was the most common reason for UR medicine use. In the subspecialties paediatric infectious diseases and gastroenterology, nearly half the medicine events were OL, while the highest frequency of UR medicine events was documented in paediatric infectious diseases (30%), cardiology and neurology (25% each). Extemporaneous and OL medicine preparations for infectious diseases (23%) are a cause for concern since the burden of paediatric disease involves mostly infections such as TB and HIV and highlights the lack of suitable paediatric-friendly medicine formulations.

The results of the survey provide evidence for UR and OL medicine use in highly specialised paediatric care. In the future, studies should be conducted to document the odds of an adverse medicine event in relation to UR and OL medicine use. Legislative changes as in the USA and Europe that compel the pharmaceutical industry to generate paediatric-specific safety and efficacy data by its inclusion in clinical trails are vitally important and recommended for the South African context.

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APPENDIX

Appendix 1. Anatomical Therapeutic Classification (ATC) of Medicines as defined by Conroy[5,15,35,38,39,49], Turner[26] and Ernest[27]

Therapeutic Class	WHO ATC	Active substance	No. of medicine events	No. of UR events	No. of OL events	Criterion for OL/UR use
A. Alimentary tract and metabolism						
A01	**Stomatological preparations**					
Antiinfectives and antiseptics for local and systemic treatment	A01AB09	Clotrimazole	2	1	1	Extemporaneous (1) route (1)
Corticosteroids for local oral treatment	A01AC01	Triamcinolone	1			
Other agents for oral treatment	A01AD02	Benzydamine	1			
A02	**Medicines for acid related disorders**					
H2 receptor antagonists	A02BA02	Ranitidine	1			
Proton pump inhibitors	A02BC01	Omperazole	14	7	9	Extemporaneous (7) Dose (6) frequency (2) age (1)
Other medicines for eptic ulcer and gastro-oesophageal reflux disease	A02BX02	Sucralfate	1	1		Not registered (1)
A03	**Medicines for functional gastrointestinal disorders**					
Propusives	A03FA01	Metoclopramide	3		1	Age (1)
	A03FA03	Domperidone	1			
A04	**Anit-emetics and anti-nauseants**					
Sertaonin antagonists	A04AA01	Ondansetron	4		1	Dose (1)
A06	**Medicines for constipation**					
Osmotically acting laxatives	A06AD11	Lactulose	8		3	Dose (2) age (1)
	A06AD17	Sodium Phosphate	1		1	Lack of paediatric data (1)
Enemas	A06AG04	Glycerol	2		1	Lack of paediatric data (1)

A07	**Anti-diarrheals, intestinal anti-inflammatory.anti-infective agents**					
Antibiotics	A07AA02	Nystatin	4			
A09	**Digestives, include. Emzymes**					
Emzyme preparations	A09AA02	Pancreatin	1	1		Extemporaneous (1)
A10	**Medicines used in diabetes**					
Insulins and analogues for injection, fast acting	A10AB01	Insulin	30			
Insulins and analogues for injection, ultra fast acting	A10AB05	Insulin	3			
Insulins and analogues for injection, intermediat acting	A10AC01	Insulin	32			
A11	**Vitamins**					
Multivitamins and other minerals, incl combinations	A11AA03	Multivitamin Syrup	80		1	Dose (1)
Vitamin A Plain	A11CA01	Retinol	4		1	Dose (1)
Vitamin D analogues	A11CC01	Ergocalciferol	15			
	A11CC03	Alphacalidiol	3			
	A11CC04	Calcitriol	1	1	1	Not registered (1) dose (1)
Vitamin B1, Plain	A11DA01	Thiamine	2		2	Dose (2)
Vitamin B complex, plain	A11EA	Vitamin B complex	1			
Other plain vitmain preparations	A11HA02	Pyridoxine	14	2	1	Extemporaneous (2) dose (1)
	A11HA03	Vitamin E	3		1	Dose (1)
	A11HA05	Biotin	1	1		Extemporaneous (1)
A12	**Mineral Supplements**					
Calcium	A12AA01	Phosphate	11	11		Extemporaneous (11)
	A12AA04	Calcium carbonate	10		1	Dose (1)
Potassium	A12BA01	Potassium chloride	16	16	2	Extemporaneous (16) dose (1) age (1)
Zinc	A12CB02	Zinc gluconate	53		32	Dose (29) indication (2) Lack of data (1)
Magnesium	A12CC01	Magnesium chloride	8	8	3	Extemporaneous (8) lack of data (2) age(1)
	A12CC02	Magnesium suphate	2	1		Not registered (1)
			333	50	62	
B. Blood and blood forming organs						
B01	**Anti-thrombotics**					
Heparin group	B01AB05	Enoxaparin sodium	1	1		Not registered (1)

Platelet aggregaion inhibitors excl. heparin	B01AC06	Asprin	1			
B02	**Anti-haemorrhagics**					
Antifibrinolytics	B02AA02	Tranexamic acid	3			
Vitamin K	B02BA01	Phytomenadione	8			
Blood coagulation factors	B02BD02	Factor 8	1			
B03	**Anti-anemic preparations**					
Iron bivalet, oral preparations	B03AA03	Ferrous lactate/salts	12	1	2	Extemporaneous (1) dose (2)
Folic acid and derivates	B03BB01	Folic Acid	20	3	15	Extemporaneous (3) dose (15)
Other anti-anemic preparations	B03XA02	Epoetin	1			
B05	**Blood substitutes and perfusion solutions**					
Blood substitutes and plasma protein fractions	B05AA01	Albumin 20%	1			
Salt solutions	B05CB04	Sodium bicarbonate	4	4		Not registered (2) Extemporaneous (2)
	B05XA03	Sodium chloride 5%	3			
			55	9	17	
C. Cardiovascular System						
C02	**Antihypertensives**					
Alph-adrenoreceptor antagonists	C02CA04	Doxazosin	1	1		Not registered (1)
C03	**Diuretics**					
Low ceiling diuretics, thiazides plain	C03AA03	Hydrochlorothiazide	1	1		Extemporaneous (1)
Highceiling diuretics, sulponamides plain	C03CA01	Furosemide	22	1	4	Extemporaneous (1) Dose (4)
Aldosterone antagonists	C03DA01	Spironolactone	16	16		Extemporaneous (16)
C07	**Beta blocking agents**					
Beta blocing agents, non selective	C07AA05	Propanolol	2			
Beta blocking agents,selective	C07AB03	Atenolol	5	5		Not registered (5)
C08	**Calcium channel blockers**					
Dihydropyridine derivatives	C08CA01	Amlodipine	7	7		Not registered (7)
	C08CA05	Nifedipine	1	1		Not registered (1)
C09	**Agents acting on the rennin-angiotensin system**					
ACE inhibitors, plain	C09AA01	Captopril	2	2		Not registered (1) extemporaneous (1)

	C09AA02	Enalapril	3	3	1	Not registered (3) indication(1)
C10	**Lipid modifying agents**					
Bile sequatrants	A10AC01	Cholestyramine	7		7	Dose (7)
			67	37	12	
D. Dermatologicals						
D01	**Anti-fungals for dermatological use**					
Antibiotics	D01AA01	Nystatin	16		1	Lack of paediatric data (1)
Antifungals for sytemic use	D01BA01	Griesofulvin	2			
D02	**Emmolients and protectives**					
Zinc poducts	D02AB	Zinc castor oil ointment	5		4	Lack of paediatric data (4)
Soft paraffin and fat products	D02AC	Aqueous cream	4			
		Haldens emulsifying base	3			
Carbamid products	D02AE51	Urea in emollient base	4		1	Lack of paediatric data (1)
D06	**Anti-biotics and chemotherapeutics for dermatological use**					
Anti-virals	D06BB03	Aciclovir	1		1	Lack of paediatric data (1)
D07	Corticosteroid dermatological preparations					
Corticosteroids, weak (Group I)	D07AA02	Hydrocortisone acetate 1%	5			
Corticosteroids, potent (Group III)	D07AC01	Bethametasone	1(2)			
D08	**Antiseptics and disinfectants**					
Iodine products	D08AG02	Povidone-iodine	1			
Silver compounds	D08AL01	Silver nitrate	1			
D09	**Medicated dressings**					
Soft parafin dressings	D09AX	S & N tulle gras dressings yellow soft parafin	1			
			43		7	
G. Genitourinary system and sex hormones						
G03	Sex hormones and modulators of the genital system					
Gonadotrophins	G03GA01	Human chorionic gonadotrophin	1	1		Not registered (1)
G04	Urologicals					
Medicines used in erectile dysfunction	G04BE03	Sildenafil	1	1	1	Extemporaneous (1) age (1)

			2	2	1	
H. Systemic hormonal preparations, excl sex hormones and insulin						
H01	**Pituatary and hypothalmic hormones and analogues**					
Vasopressin and analogues	H01BA02	Desmopressin	2		1	Dose (1)
H02	Corticosteroids for sytemic use					
Glucocorticoids	H02AB01	Bethametasone	1			
	H02AB02	Dexamethasone	7	2	3	Not registered (2) Dose (1) indication (1) route (1)
	H02AB04	Methlyprednisone	7		5	Dose (4) route (1)
	H02AB06	Prednisone	52		14	Indication (9) Dose (5)
	H02AB07	Prednisolone	3		2	Indication (2)
	H02AB09	Hydrocortisone	2		2	Indication (1) dose (1)
H03	**Thyroid therapy**					
Thyroid hormones	H03AA01	Levothyroxine sodium	4			
H04	**Pancreatic hormones**					
Glycogenoltyic hormones	H04AA01	Glucagon	1			
			79	2	27	
J. Anti-infectives for systemic use						
J01	**Anti-bacterials for systemic use**					
Penicillins with extended spectrum	J01CA01	Ampicillin	12		3	Dose (3)
	J01CA04	Amoxicillin	14		1	Dose (1)
Beta lactamase sensitive penicillins	J01CE01	Benyl Penicillin	2		1	Dose (1)
Beta lactamase resistant penicillins	J01CF02	Cloxacillin	2			
	J01CF05	Flucloxacillin	1			
Combination of penicillins, including beta lactamase inhibitors	J01CR02	Amoxycillin/clavulanic acid	11		2	Dose (2)
	J01CR05	Piperacillin with tazobactam	14		5	Dose (5)
Second generation Cephalosporins	J01DC02	Cefuroxamine	25		4	Dose(4)
Third generation cephalosporin	J01DD01	Cefotaxime	9		4	Dose (4)
	J01DD04	Ceftriaxone	18		14	Dose (14)
Carbapenems	J01DH02	Meropenem	11		3	Dose (2) age (1)
	J01DH03	Ertapenem	12		10	Dose (8) age (2)

Combination of sulphonamides and trimethoprim, incl. derivates	J01EE01	Co-trimoxazole	33		14	Dose (13) indication (1)
Macrolides	J01FA01	Erythromycin	4	1		Extemporaneous (1)
	J01FA10	Azithromycin	3			
Other aminogycosides	J01GB03	Gentamycin	19		13	Dose (6) route (6) frequency (1)
Other aminogycosides	J01GB06	Amikacin	24		14	Dose (13) indication (1)
Flouroquinolones	J01MA01	Ofloxacin	15	15		Not registered (15)
	J01MA02	Ciprofloxacin	1			
Glycopeptide antibacterials	J01XA01	Vancomycin	9		4	Dose (3) age (1)
Polymyxins	J01XB01	Colistin	1	1		Not registered
J02	**Antimycotics for systemic use**					
Antibiotics	J02AA01	Amphoterican B	1		1	Dose (1)
Triazole derivative	J02AC01	Fluconazole	15		2	Dose (2)
J04	**Antimycobacterials**					
Antibiotics	J04AB02	Rifampicin	31		2	Dose (1) age(1)
Hydrazides	J04AC01	Isoniazid	53	49	21	Extemporaneous (49) dose (21)
Thiocarbamide derivatives	J04AD03	Ethionamide	25	24	2	Extemporaneous (24) dose (1) age (1)
Other Medicines for the treatment of tuberculosis	J04AK01	Pyrazinamide	36	34	7	Extemporaneous (34) dose (5) age (2)
	J04AK02	Ethambutol	28	27	2	Extemporaneous (27) dose (1) age (1)
	J04AK03	Terizidone	12	1	10	Extemproaneous (1) dose (10)
Combinations of medicines for treatment of tuberculosis	J04AM02	Rifampicin and Isoniazide	4		2	Dose (2)
	J04AM05	Rifampicin, Isoniazide,pyrazinamide	10	2	4	Not registered (1) Extemporaneous (1)Dose (4)
	J04AM06	Rifampicin, isoniziazid,pyrazinamide and ethambutol	1		1	Age (1)
Medicines for the treatment of lepra	J04BA02	Dapsone	3	1	3	Extemproaneous (1) Dose (3)
J05	**Antivirals for systemic use**					
Nucleoside and nucleotides excl. reverse transcriptase inhibitors	J05AB01	Aciclovir	8		2	Dose (2)
	J05AB06	Ganciclovir	7		2	Dose (1) frequency (1)
	J05AB14	Valganciclovir	1			

Protease Inhibitors	J05AE03	Ritonavir	10	8	4	Not registered (8) age (3) dose (1)
Nucleoside and nucleotide reverse transcriptase inhibitors	J05AF01	Zidovudine	1			
	J05AF04	Stavudine	5	1	5	Extemporaneous (1) dose (4) age (1)
	J05AF05	Lamivudine	26		20	Dose (20)
	J05AF06	Abacavir	22		16	Dose (16)
Non-nucleoside reverse transcriptase inhibitors	J05AG01	Nevirapine	7		2	Dose (2)
	J05AG03	Efavirenz	5		4	Dose (4)
Antivirals for the treatment of HIV infections combinations of NTRIs/NNRTIs	J05AR01	Zidovine and lamivudine	1		1	Dose (1)
Antivirals for the treatment of HIV infections combinations of protease inhibitors	J05AR10	Lopinovir-ritonavir	21		18	Dose (18)
J06	**Immune sera and immunoglobulins**					
Immunoglobulins, normal human	J06BA02	Intravenous Immunoglobulins	6		3	Dose (3)
J07	**Vaccines**					
Pneumococcal vaccines	J07AL02	Pneumococcus, purified polysaccharide antigen conjugated	1			
Hepatitis Vaccines	J07BC01	Hepatitis B Vaccine	1			
Bacterial and viral vaccines, combined	J07CA06	DTaP-IPV/Hib	1			
			582	164	226	
L. Anti-neoplastic and immunomodulating agents						
L01	**Antineoplatic agents**					
Nitrogen mustard analogues	L01AA01	Cyclophosphamide	5		1	Dose (1)
Folic acid analogues	L01BA01	Methotrexate	4		2	Dose (1) indication (1)
Purine anologues	L01BB02	Mercaptopurine	1			
Pyrimidine analogues	L01BC01	Cytarabine	10		4	Lack of paediatric data (3) Indication (1)
Vinca alkaloids and analogues	L01CA02	Vincristine	9			
Podophyllotoxin derivates	L01CB01	Etoposide	5	5		Not registered (5)
Platinum comounds	L01XA02	Carboplatin	2	2		Not registered (2)
Other antineoplastic agents	L01XX02	Asparginase	8			
	L01XX05	Hydroxyurea/hydroxycarbamide	1	1		Not registered (1)
L04	**Immunosupressants**					
Tumor necrosis factor alpha inhibitors	L04AB01	Etanercept	2			

Interleukin inhibitors	L04AC07	Tocilizumab	1		1	Dose (1)
Other Immunosupressants	L04AX02	Thalidomide	1	1		Not registered (1)
	L04AX03	Methotrexate	4		2	Dose (1) indication (1)
			53	9	10	
M. Musculoskelatal system						
M01	**Anti-inflammatory and anti-rheumatic products**					
Acetic acis derivatives and related substances	M01AB05	Diclofenac	1			
Proprionic Acid Derivates	M01AE01	Brufen	16		7	Dose (6) age (1)
M03	Muscle relaxants					
Other quaternaty ammonium compounds	M03AC01	Pancuronium	2			
Other centrally acting agents	M03BX01	Baclofen	2		1	Dose (1)
MO4	**Anti-gout preparations**					
Preparations inhibiting uric acid production	M04AA01	Allopurinol	1		1	Route (1)
M05	**Medicines for the treatment of bone diseases**					
Bisphosphonates	M05BA03	Pamidronic Acid	3	3		Not registered (3)
			25	3	9	
N. Nervous System						
N01	**Anesthetics**					
Other general anesthetics	N01AX03	Ketamine	12		1	Dose (1)
N02	**Analgesics**					
Natural opoid alkaloids	N02AA01	Morphine	8	6		Extemporaneous (6)
Other opoids	N02AX01	Tilidine	16		2	Dose (1) frequency (1)
Anilides	N02BE01	Paracetamol	74	1	11	Extemporaneous (1) dose (10) lack of paediatric data (1)
Other anti migrane preparations	N02CX02	Clonidine	6	6		Not registered (4) extemporaneous (2)
N03	**Anti-epileptics**					
Barbiturates and derivates	N03AA02	Phenobarbital	16			
Phenylpiperidine derivates	N03AB02	Phenytoin	2			
Fatty Acid Derivates	N03AG01	Valproic Acid	9		3	Dose (3)
Benzodiazepine derivatives	N03AE01	Clonazepam	5			
Carboxamide derivatives	N03AF01	Carbamazepine	3			

Other antiepileptics	N03AX09	Lamotrigine	2		1	Dose (1)
N05	**Psycholeptics**					
Phenothiazines with aliphatic side chains	N05AA01	Chlorpromazine	1	1	1	Extemporaneous (1) dose(1)
Benzodiazepine derivatives	N05BA01	Diazepam	17		7	Dose (5) contra-indication (1) route(1)
	N05BA06	Lorazepam	2		1	Dose (1)
	N05BA09	Clobazam	2	2		Not registered (2)
Diphenylmethane derivates	N05BB01	Hydroxyzine	1		1	Dose (1)
Aldehydes and derivates	N05CC01	Chloral Hydrate	3		3	Contra-indication (3)
Benzodiazepine derivatives	N05CD08	Midazolam	4		2	Indication (2)
N06	**Psychoanaleptics**					
Selective seratonin reuptake inhibitors	N06AB03	Fluoxetine	5	3	3	Extemporaneous (3) Dose (3)
			188	19	36	
P. Anti-parasitic products, insecticides and repellents						
P01	**Anti-protozoals**					
Nitroimidazole derivatives	P01AB01	Metranidazole	8		2	Dose (2)
Aminoquinolones	P01BA01	Cloroquine	2		2	Dose (2)
P02	**Anthelmintics**					
Benzimidazole derivates	P02CA01	Mebendazole	1			
	P02CA03	Albendazole	1		1	Age (1)
P03	**Ectoparasites, incl. scabicides, insecticides and repellents**					
Sulfur containing product	P03AA04	Sulfiram	1			
Other ectoparasiticides, incl scabicides	P03AX01	Benzyl benzoate	1		1	Age (1)
			14		6	
R. Respiratory system						
RO1	**Nasal Preparations**					
Sympathomimetics, plain	R01AA05	Oxymetazolin	6		1	Age (1)
Corticosteroids	R01AD01	Becloetasone	1			
other nasal preparations	R01AX10	Sodium Chloride	10	1	1	Not registered (1) dose (1)
RO2	**Throat preparations**					
Antiseptics	R02AA15	Povidone-iodine	1			
RO3	**Medicines for obstuctive airway disease**					

Alpha - and beta adrenoreceptor agonist	R03AA01	Epinephrine	6		2	Age (1) dose (1)
Selective Beta 2 adrenoreceptor agonists	R03AC02	Salbutamol	5			
	R03AC04	Fenoterol	9		10	Age (6) dose (2) frequency (2)
Glucocorticoids	R03BA02	Budesonide	8			
Anticholinergics	R03BB01	Ipratropium Bromide	1		1	Age (1)
RO6	**Anti-histamines for systemic use**					
Piperazine derivatives	R06AE07	Cetirizine	1			
Substituted alkylamines	R06AB04	Chlorphenamine	1		1	Dose (1)
			49	1	16	
S. Sensory Organs						
S01	**Opthalmologicals**					
Antibiotics	S01AA01	Chloramphenicol eye ointment	2		2	Contraidication (1) lack of paediatric data (1)
	S01AX11	Ofloxacin	3		1	Indication (1)
Carbonic anhydrase inhibitors	S01EC01	Acetazolomide	2			
Sympathomimmetics used as decongestants	S01GA52	Tetryzoline with antazoline	1			
Visceoelastic Substances	S01KA02	Hypromellose	1			
			9		3	
V. Various						
V03	**All other therapeutic products**					
Medicines for the treatment of hyperkalemia and hyperphosphatemia	V03AE01	Polystyrene sulfonate	3			
Detoxifying agents for antineoplastic treatment	V03AF03	Folinic Acid	1	1		Not registered (1)
V04	**Diagnostic agents**					
Tests for diabetes	V04CA02	Glucose	1			
Tests for pituitary function	V04CD01	Metyrapone	3	3		Not registered (3)

Appendix 2: Anatomic Therapeutic Classification (ATC) classification of medicines as defined by the Delphi Survey[6]

Therapeutic Class	WHO ATC	Active substance	No. of medicine events	No. of UR events	No. of OL events	Criterion for OL/UR use
A. Alimentry tract and metabolism						
A01	**Stomatological preparations**					
Antiinfectives and antiseptics for local and systemic treatment	A01AB09	Clotrimazole	2		2	Extemporaneous (1) route (1)
Corticosteroids for local oral treatment	A01AC01	Triamcinolone	1			
Other agents for oral treatment	A01AD02	Benzydamine	1			
A02	**Medicines for acid related disorders**					
H2 receptor antagonists	A02BA02	Ranitidine	1			
Proton pump inhibitors	A02BC01	Omperazole	14		16	Extemporaneous (7) Dose (6) frequency (2) age (1)
Other medicines for eptic ulcer and gastro-oesophageal reflux disease	A02BX02	Sucralfate	1	1		Not registered (1)
A03	**Medicines for functional gastrointestinal disorders**					
Propusives	A03FA01	Metoclopramide	3		1	Age (1)
	A03FA03	Domperidone	1			
A04	**Anit-emetics and anti-nauseants**					
Sertaonin antagonists	A04AA01	Ondansetron	4		1	Dose (1)
A06	**Medicines for constipation**					
Osmotically acting laxatives	A06AD11	Lactulose	8		3	Dose (2) age (1)
	A06AD17	Sodium Phosphate	1		1	Lack of paediatric data (1)
Enemas	A06AG04	Glycerol	2		1	Lack of paediatric data (1)
A07	**Anti-diarrheals, intestinal anti-inflammatory.anti-infective agents**					
Antibiotics	A07AA02	Nystatin	4			
A09	**Digestives, include. Emzymes**					
Emzyme preparations	A09AA02	Pancreatin	1		1	Extemporaneous (1)
A10	**Medicines used in diabetes**					

Insulins and analogues for injection, fast acting	A10AB01	Insulin	30			
Insulins and analogues for injection, ultra fast acting	A10AB05	Insulin	3			
Insulins and analogues for injection, intermediat acting	A10AC01	Insulin	32			
A11	**Vitamins**					
Multivitamins and other minerals, incl combinations	A11AA03	Multivitamin Syrup	80		1	Dose(1)
Vitamin A Plain	A11CA01	Retinol	4		1	Dose(1)
Vitamin D analogues	A11CC01	Ergocalciferol	15			
	A11CC03	Alphacalidiol	3			
	A11CC04	Calcitriol	1	1	1	Not registered (1) dose (1)
Vitamin B1, Plain	A11DA01	Thiamine	2		2	Dose (2)
Vitamin B complex, plain	A11EA	Vitamin B complex	1			
Other plain vitmain preparations	A11HA02	Pyridoxine	14		3	Extemporaneous (2) dose (1)
	A11HA03	Vitamin E	3		1	Dose (1)
	A11HA05	Biotin	1		1	Extemporaneous (1)
A12	**Mineral Supplements**					
Calcium	A12AA01	Phosphate	11		11	Extemporaneous (11)
	A12AA04	Calcium carbonate	10		1	Dose (1)
Potassium	A12BA01	Potassium chloride	16		18	Extemporaneous (16) dose(1) age (1)
Zinc	A12CB02	Zinc gluconate	53		32	Dose (29) indication (2) Lack of data (1)
Magnesium	A12CC01	Magnesium chloride	8		11	Extemporaneous (8) lack of data (2) age (1)
	A12CC02	Magnesium suphate	2	1		Not registered (1)
			333	3	109	
B. Blood and blood forming organs						
B01	**Anti-thrombotics**					
Heparin group	B01AB05	Enoxaparin sodium	1	1		Not registered (1)
Platelet aggregaion inhibitors excl. heparin	B01AC06	Asprin	1			
B02	**Anti-haemorrhagics**					

Antifibrinolytics	B02AA02	Tranexamic acid	3			
Vitamin K	B02BA01	Phytomenadione	8			
Blood coagulation factors	B02BD02	Factor 8	1			
B03	**Anti-anemic preparations**					
Iron bivalet, oral preparations	B03AA03	Ferrous lactate/salts	12	1	3	Extemporaneous (1) dose (2)
Folic acid and derivates	B03BB01	Folic Acid	20		18	Extemporaneous (3) dose(15)
Other anti-anemic preparations	B03XA02	Epoetin	1			
B05	**Blood substitutes and perfusion solutions**					
Blood substitutes and plasma protein fractions	B05AA01	Albumin 20%	1			
Salt solutions	B05CB04	Sodium bicarbonate	4	2	2	Not registered (2) Extemporaneous (2)
	B05XA03	Sodium chloride 5%	3			
			55	4	23	
C. Cardiovascular System						
C02	**Antihypertensives**					
Alph-adrenoreceptor antagonists	C02CA04	Doxazosin	1	1		Not registered (1)
C03	**Diuretics**					
Low ceiling diuretics, thiazides plain	C03AA03	Hydrochlorothiazide	1		1	Extemporaneous (1)
Highceiling diuretics, sulponamides plain	C03CA01	Furosemide	22		5	Extemporaneous (1) Dose(4)
Aldosterone antagonists	C03DA01	Spironolactone	16		16	Extemporaneous (16)
C07	**Beta blocking agents**					
Beta blocing agents, non selective	C07AA05	Propanolol	2			
Beta blocking agents,selective	C07AB03	Atenolol	5	5		Not registered (5)
C08	**Calcium channel blockers**					
Dihydropyridine derivatives	C08CA01	Amlodipine	7	7		Not registered (7)
	C08CA05	Nifedipine	1	1		Not registered (1)
C09	**Agents acting on the rennin-angiotensin system**					
ACE inhibitors, plain	C09AA01	Captopril	2	1	1	Not registered (1) extemporaneous (1)
	C09AA02	Enalapril	3	3	1	Not registered (3) indication(1)

C10	**Lipid modifying agents**					
Bile sequatrants	A10AC01	Cholestyramine	7		7	Dose (7)
			67	18	31	
D. Dermatologicals						
D01	**Anti-fungals for dermatological use**					
Antibiotics	D01AA01	Nystatin	16		1	Lack of paediatric data (1)
Antifungals for sytemic use	D01BA01	Griesofulvin	2			
D02	**Emmolients and protectives**					
Zinc poducts	D02AB	Zinc castor oil ointment	5		4	Lack of paediatric data (4)
Soft paraffin and fat products	D02AC	Aqueous cream	4			
		Haldens emulsifying base	3			
Carbamid products	D02AE51	Urea in emollient base	4		1	Lack of paediatric data (1)
D06	**Anti-biotics and chemotherapeutics for dermatological use**					
Anti-virals	D06BB03	Aciclovir	1		1	Lack of paediatric data (1)
D07	Corticosteroid dermatological preparations					
Corticosteroids, weak (Group I)	D07AA02	Hydrocortisone acetate 1%	5			
Corticosteroids, potent (Group III)	D07AC01	Bethametasone	1(2)			
D08	**Antiseptics and disinfectants**					
Iodine products	D08AG02	Povidone-iodine	1			
Silver compounds	D08AL01	Silver nitrate	1			
D09	**Medicated dressings**					
Soft parafin dressings	D09AX	S & N tulle gras dressings yellow soft parafin	1			
			43		7	
G. Genitourinary system and sex hormones						
G03	Sex hormones and modulators of the genital system					
Gonadotrophins	G03GA01	Human chorionic gonadotrophin	1	1		Not registered (1)
G04	Urologicals					
Medicines used in erectile dysfunction	G04BE03	Sildenafil	1		2	Extemporaneous (1) age (1)

			2	1	2	
H. Systemic hormonal preparations, excl sex hormones and insulin						
H01	**Pituatary and hypothalmic hormones and analogues**					
Vasopressin and analogues	H01BA02	Desmopressin	2		1	Dose (1)
H02	Corticosteroids for sytemic use					
Glucocorticoids	H02AB01	Bethametasone	1			
	H02AB02	Dexamethasone	7	2	3	Not registered (2) Dose (1) indication (1) route (1)
	H02AB04	Methlyprednisone	7		5	Dose (4) route (1)
	H02AB06	Prednisone	52		14	Indication (9) Dose (5)
	H02AB07	Prednisolone	3		2	Indication (2)
	H02AB09	Hydrocortisone	2		2	Indication (1) dose (1)
H03	**Thyroid therapy**					
Thyroid hormones	H03AA01	Levothyroxine sodium	4			
H04	**Pancreatic hormones**					
Glycogenoltyic hormones	H04AA01	Glucagon	1			
			79	2	27	
J. Anti-infectives for systemic use						
J01	**Anti-bacterials for systemic use**					
Penicillins with extended spectrum	J01CA01	Ampicillin	12		3	Dose (3)
	J01CA04	Amoxicillin	14		1	Dose (1)
Beta lactamase sensitive penicillins	J01CE01	Benyl Penicillin	2		1	Dose (1)
Beta lactamase resistant penicillins	J01CF02	Cloxacillin	2			
	J01CF05	Flucloxacillin	1			
Combination of penicillins, including beta lactamase inhibitors	J01CR02	Amoxycillin/clavulanic acid	11		2	Dose (2)
	J01CR05	Piperacillin with tazobactam	14		5	Dose (5)
Second generation Cephalosporins	J01DC02	Cefuroxamine	25		4	Dose(4)
Third generation cephalosporin	J01DD01	Cefotaxime	9		4	Dose (4)
	J01DD04	Ceftriaxone	18		14	Dose (14)

Carbapenems	J01DH02	Meropenem	11		3	Dose (2) age (1)
	J01DH03	Ertapenem	12		10	Dose (8) age (2)
Combination of sulphonamides and trimethoprim, incl. derivates	J01EE01	Co-trimoxazole	33		14	Dose (13) indication (1)
Macrolides	J01FA01	Erythromycin	4		1	Extemporaneous (1)
	J01FA10	Azithromycin	3			
Other aminogycosides	J01GB03	Gentamycin	19		13	Dose (6) route (6) frequency (1)
Other aminogycosides	J01GB06	Amikacin	24		14	Dose(13) indication(1)
Flouroquinolones	J01MA01	Ofloxacin	15	15		Not registered (15)
	J01MA02	Ciprofloxacin	1			
Glycopeptide antibacterials	J01XA01	Vancomycin	9		4	Dose (3) age (1)
Polymyxins	J01XB01	Colistin	1	1		Not registered
J02	**Antimycotics for systemic use**					
Antibiotics	J02AA01	Amphoterican B	1		1	Dose (1)
Triazole derivative	J02AC01	Fluconazole	15		2	Dose (2)
J04	**Antimycobacterials**					
Antibiotics	J04AB02	Rifampicin	31		2	Dose (1) age(1)
Hydrazides	J04AC01	Isoniazid	53		70	Extemporaneous (49) dose (21)
Thiocarbamide derivatives	J04AD03	Ethionamide	25		26	Extemporaneous (24) dose (1) age (1)
Other Medicines for the treatment of tuberculosis	J04AK01	Pyrazinamide	36		41	Extemporaneous (34) dose (5) age (2)
	J04AK02	Ethambutol	28		29	Extemporaneous (27) dose (1) age (1)
	J04AK03	Terizidone	12		11	Extemproaneous (1) dose (10)
Combinations of medicines for treatment of tuberculosis	J04AM02	Rifampicin and Isoniazide	4		2	Dose (2)
	J04AM05	Rifampicin, Isoniazide,pyrazinamide	10		5	Not registered (1) Extemporaneous (1)Dose (4)
	J04AM06	Rifampicin, isoniziazid,pyrazinamide and ethambutol	1		1	Age (1)
Medicines for the treatment of lepra	J04BA02	Dapsone	3		4	Extemporaneous (1) Dose (3)
J05	**Antivirals for systemic use**					
Nucleoside and nucleotides excl. reverse transcriptase inhibitors	J05AB01	Aciclovir	8		2	Dose (2)

	J05AB06	Ganciclovir	7		2	Dose (1) frequency (1)
	J05AB14	Valganciclovir	1			
Protease Inhibitors	J05AE03	Ritonavir	10	8	4	Not registered (8) age (3) dose (1)
Nucleoside and nucleotide reverse transcriptase inhibitors	J05AF01	Zidovudine	1			
	J05AF04	Stavudine	5		6	Extemporaneous (1) dose (4) age (1)
	J05AF05	Lamivudine	26		20	Dose (20)
	J05AF06	Abacavir	22		16	Dose (16)
Non-nucleoside reverse transcriptase inhibitors	J05AG01	Nevirapine	7		2	Dose (2)
	J05AG03	Efavirenz	5		4	Dose (4)
Antivirals for the treatment of HIV infections combinations of NTRIs/NNRTIs	J05AR01	Zidovine and lamivudine	1		1	Dose (1)
Antivirals for the treatment of HIV infections combinations of protease inhibitors	J05AR10	Lopinovir-ritonavir	21		18	Dose (18)
J06	**Immune sera and immunoglobulins**					
Immunoglobulins, normal human	J06BA02	Intravenous Immunoglobulins	6		3	Dose (3)
J07	**Vaccines**					
Pneumococcal vaccines	J07AL02	Pneumococcus, purified polysaccharide antigen conjugated	1			
Hepatitis Vaccines	J07BC01	Hepatitis B Vaccine	1			
Bacterial and viral vaccines, combined	J07CA06	DTaP-IPV/Hib	1			
			582	24	365	
L. Anti-neoplastic and immunomodulating agents						
L01	**Antinoeplatic agents**					
Nitrogen mustard analogues	L01AA01	Cyclophosphamide	5		1	Dose (1)
Folic acid analogues	L01BA01	Methotrexate	4		2	Dose (1) indication (1)
Purine anologues	L01BB02	Mercaptopurine	1			
Pyrimidine analogues	L01BC01	Cytarabine	10		4	Lack of paediatric data (3) Indication (1)
Vinca alkaloids and analogues	L01CA02	Vincristine	9			
Podophyllotoxin derivates	L01CB01	Etoposide	5	5		Not registered (5)
Platinum comounds	L01XA02	Carboplatin	2	2		Not registered (2)

Other antineoplastic agents	L01XX02	Asparginase	8			
	L01XX05	Hydroxyurea/hydroxycarbamide	1	1		Not registered (1)
L04	**Immunosupressants**					
Tumor necrosis factor alpha inhibitors	L04AB01	Etanercept	2			
Interleukin inhibitors	L04AC07	Tocilizumab	1		1	Dose (1)
Other Immunosupressants	L04AX02	Thalidomide	1	1		Not registered (1)
	L04AX03	Methotrexate	4		2	Dose (1) indication (1)
			53	9	10	
		M. Musculoskelatal system				
M01	**Anti-inflammatory and anti-rheumatic products**					
Acetic acis derivatives and related substances	M01AB05	Diclofenac	1			
Proprionic Acid Derivates	M01AE01	Brufen	16		7	Dose (6) age (1)
M03	Muscle relaxants					
Other quaternaty ammonium compounds	M03AC01	Pancuronium	2			
Other centrally acting agents	M03BX01	Baclofen	2		1	Dose (1)
MO4	**Anti-gout preparations**					
Preparations inhibiting uric acid production	M04AA01	Allopurinol	1		1	Route (1)
M05	**Medicines for the treatment of bone diseases**					
Bisphosphonates	M05BA03	Pamidronic Acid	3	3		Not registered (3)
			25	3	9	
		N. Nervous System				
N01	**Anesthetics**					
Other general anesthetics	N01AX03	Ketamine	12		1	Dose (1)
N02	**Analgesics**					
Natural opoid alkaloids	N02AA01	Morphine	8		6	Extemporaneous (6)
Other opoids	N02AX01	Tilidine	16		2	Dose (1) frequency (1)
Anilides	N02BE01	Paracetamol	74		12	Extemporaneous (1) dose (10) lack of paediatric data (1)
Other anti migrane preparations	N02CX02	Clonidine	6	4	2	Not registered (4) extemporaneous (2)

N03	**Anti-epileptics**					
Barbiturates and derivates	N03AA02	Phenobarbital	16			
Phenylpiperidine derivates	N03AB02	Phenytoin	2			
Fatty Acid Derivates	N03AG01	Valproic Acid	9		3	Dose (3)
Benzodiazepine derivatives	N03AE01	Clonazepam	5			
Carboxamide derivatives	N03AF01	Carbamazepine	3			
Other antiepileptics	N03AX09	Lamotrigine	2		1	Dose (1)
N05	**Psycholeptics**					
Phenothiazines with aliphatic side chains	N05AA01	Chlorpromazine	1		2	Extemporaneous (1) dose(1)
Benzodiazepine derivatives	N05BA01	Diazepam	17		7	Dose (5) contra-indication (1) route (1)
	N05BA06	Lorazepam	2		1	Dose (1)
	N05BA09	Clobazam	2	2		Not registered (2)
Diphenylmethane derivates	N05BB01	Hydroxyzine	1		1	Dose (1)
Aldehydes and derivates	N05CC01	Chloral Hydrate	3		3	Contra-indication (3)
Benzodiazepine derivatives	N05CD08	Midazolam	4		2	Indication (2)
N06	**Psychoanaleptics**					
Selective seratonin reuptake inhibitors	N06AB03	Fluoxetine	5		6	Extemporaneous (3) Dose (3)
			188	6	49	
P. Anti-parasitic products, insecticides and repellents						
P01	**Anti-protozoals**					
Nitroimidazole derivatives	P01AB01	Metranidazole	8		2	Dose (2)
Aminoquinolones	P01BA01	Cloroquine	2		2	Dose (2)
P02	**Anthelmintics**					
Benzimidazole derivates	P02CA01	Mebendazole	1			
	P02CA03	Albendazole	1		1	Age (1)
P03	**Ectoparasites, incl. scabicides, insecticides and repellents**					
Sulfur containing product	P03AA04	Sulfiram	1			
Other ectoparasiticides, incl scabicides	P03AX01	Benzyl benzoate	1		1	Age (1)

			14		6	
R. Respiratory system						
RO1	**Nasal Preparations**					
Sympathomimetics, plain	R01AA05	Oxymetazolin	6		1	Age (1)
Corticosteroids	R01AD01	Becloetasone	1			
other nasal preparations	R01AX10	Sodium Chloride	10	1	1	Not registered (1) dose (1)
RO2	**Throat preparations**					
Antiseptics	R02AA15	Povidone-iodine	1			
RO3	**Medicines for obstuctive airway disease**					
Alpha - and beta adrenoreceptor agonist	R03AA01	Epinephrine	6		2	Age (1) dose (1)
Selective Beta 2 adrenoreceptor agonists	R03AC02	Salbutamol	5			
	R03AC04	Fenoterol	9		10	Age (6) dose (2) frequency (2)
Glucocorticoids	R03BA02	Budesonide	8			
Anticholinergics	R03BB01	Ipratropium Bromide	1		1	Age (1)
RO6	**Anti-histamines for systemic use**					
Piperazine derivatives	R06AE07	Cetirizine	1			
Substituted alkylamines	R06AB04	Chlorphenamine	1		1	Dose (1)
			49	1	16	
S. Sensory Organs						
S01	**Opthalmologicals**					
Antibiotics	S01AA01	Chloramphenicol eye ointment	2		2	Contraindication (1) lack of paediatric data (1)
	S01AX11	Ofloxacin	3		1	Indication (1)
Carbonic anhydrase inhibitors	S01EC01	Acetazolomide	2			
Sympathomimmetics used as decongestants	S01GA52	Tetryzoline with antazoline	1			
Visceoelastic Substances	S01KA02	Hypromellose	1			
			9		3	
V. Various						
V03	**All other therapeutic products**					

Medicines for the treatment of hyperkalemia and hyperphosphatemia	V03AE01	Polystyrene sulfonate	3			
Detoxifying agents for antineoplastic treatment	V03AF03	Folinic Acid	1	1		Not registered (1)
V04	**Diagnostic agents**					
Tests for diabetes	V04CA02	Glucose	1			
Tests for pituitary function	V04CD01	Metyrapone	3	3		Not registered (3)
			8	4		